Acta Pædiatrica

Vol. 42 · March 1953 · No 2

INDEX

Asthmatic Bronchitis in Children 87
I. Boesen

Coeliac Disease. III. Excretion of Unsaturated and Saturated Fatty Acids by Patients with Coeliac Disease 97
H. A. Weijers and J. H. van de Kamer

Further Studies of Tuberculin Hemagglutination in Tuberculous Infection, Benign and Virulent 113
R. Lagercrantz, J. C. Peterson and J. Lind

On Plasma Calcium in Cord Blood and in the Newborn 126
N. Hallman and I. Salmi

On Psychogenic Obesity in Children. II 130
N. Juel-Nielsen

The Supply of Oxygen to Prematures and the Appearance of Retrolental Fibroplasia 147
A. Huggert

A Hyperacute Case of Erythroleukaemia Treated with Aminopterin 157
K. Lien-Keng

Oto-Rhinological Infections in Childhood 166
G. Tunevall

Proceedings of the Section for Pediatrics and School Hygiene of the Swedish Medical Society 168

Book Review 177

News and Comments 178

Almqvist & Wiksells Boktryckeri AB UPPSALA

ACTA PÆDIATRICA

The ACTA PÆDIATRICA publishes papers on scientific and clinical investigations in the field of pediatrics. These papers are published in English, French, or German, according to the wishes of the author. Each number consists of about 5–6 printed sheets, 6 numbers forming one volume. The numbers will be issued every second month. The Acta Pædiatrica is open to papers from authors in all countries. Manuscripts for publication, books for review, and correspondence relating to the editorial management should be sent to *Prof. Arvid Wallgren, Chief Editor, Karolinska Sjukhusets Barnklinik, Stockholm 60, Sweden.* Papers are accepted for publication on condition that they are contributed solely to the Acta Pædiatrica. They are subject to editorial revision. The paper should preferably not exceed 16 printed pages including space for figures and tables. Monographs and more extensive articles are published separately as supplements at the author's own expenses. These supplements will be delivered to subscribers free of charge. Manuscripts are published in the order received, but the Editor reserves the right to change this order when advisable.

Manuscripts should be type-written, double spaced with reasonably wide margins. A summary should be included. A complete bibliography must be added and must conform exactly to the style of the *Quarterly Cumulative Index Medicus* giving name of author, initials, full title of the paper, and abbreviated name of the journal, with volume, page, and year. References to books and monographs should indicate the author, the title, the name and city of the publisher, the year of publication, and the edition. References must be listed alphabetically. Illustrations (marked with the author's name) and tables accompanying manuscripts should be numbered, provided with suitable, short legends and so arranged that they are comprehensible to the reader without reference to the text.

Tables and figures that exceed 3 pages in the original papers and 2 pages in the case reports are printed at the expenses of the author.

Galley proofs will be sent to the principal author from the printer to be returned to the Editor together with the manuscript when corrections are completed. Reprints of articles published must be ordered specifically in separate communications to the publishers Almqvist & Wiksell, Uppsala, Sweden. All communications in regard to advertising, subscription, change of address, etc., should also be sent to the publishers. Checks, money orders, and drafts should be made payable to the publishers. Subscription price Sw. cr. 45:— pr volume postage included.

Acta Pædiatrica **42**: 87—96. March 1953

From the Municipal Children's Allergy Clinic at the Queen Louises Children's Hospital, Copenhagen. Chief: E. W. Flensborg, M. D.

Asthmatic Bronchitis in Children

Prognosis for 162 cases, observed 6—11 years

by IB BOESEN

In childhood you will often meet the type of bronchitis that is produced by respiratory congestion and is characterized by prolonged expiration and numerous rales in both lungs. It is called asthmatic bronchitis (in Anglo-Saxon literature often "spasmodic bronchitis") owing to the clinical likeness to asthma bronchiale.

It is often difficult in infancy to distinguish between asthmatic bronchitis and asthma bronchiale; it is not possible by definition to set up distinct criteria (1). The main differences are the attacks of dyspnoea, that characterize asthma bronchiale and the more chronic recurrent cough, which is characteristic for a case of bronchitis. Common to both are the stethoscopic findings of prolonged expiration and characteristic rales. The change between the 2 conditions is not distinct and is often intermingled, especially the older the patient becomes.

Judging from opinions in the literature it would appear that there is no special relation between asthmatic bronchitis and asthma bronchiale in children (e.g. 4 and 7), and that the similarity in the clinical picture does not mean that there is a marked uniformity regarding the aetiology and pathology. One is inclined to deny the fact that asthmatic bronchitis is a specific-allergic reaction as one seldom sees a positive cutaneous reaction or a positive provocation test in these patients. The presence of bacterial allergy as the cause of asthma bronchiale has been supported by COOKE in the first place (6). From Scandinavia there are papers on this subject concerning adult patients by KOBRO (10), and in the case of children by FLENSBORG *et al.* (9). One may assume, that asthmatic bronchitis in children is in many cases a bacterial-allergic reaction of the mucous membranes and, if this is so the condition may be suitable for therapy with bacterial vaccines, as FLENSBORG *et al.* (9) have shown that favourable results may be obtained by the treatment of the bacterial-allergic conditioned asthma bronchiale in children.

TABLE 1

Number of children admitted with the diagnosis asthmatic bronchitis in the Children's Hospital, Fuglebakken, and Sundby Hospital's Children's Ward 1940—45; examined by questionaire forms in 1951 with regard to the subsequent development of asthma bronchiale.

Age when admission with asthmatic bronch.	Number of questionaire forms answered	Number of pats not traced after the dates stated	Dead	Total	Percentage number of answers	Subsequent development of asthma bronchiale
0—5 months ..	31	3	3	37	84	1
6—11 » ..	54	3	1	58	93	4
1—2[11]/12 years	44	5	0	49	88	8
≧ 3 years	33	8	0	41	82	14
Total	162	19	4	185	88	27

TABLE 2

Number of children admitted with the diagnosis asthmatic bronchitis in the Children's Hospital Fuglebakken, and Sundby Hospital's Children's Ward 1940—45, examined by questionaire forms in 1951 with reference to the development of asthma bronchiale.

Age on admission with asthmatic bronch.	♂	♀	Total	♂ %	♀ %	Subsequent development of asthma		
						♂	♀	♂ + ♀
0—5 months ..	19	12	31	61	39	1 = 5 %	0	3 %
6—11 » ..	35	19	54	65	35	3 = 9 %	1 = 5 %	7 %
1—2[11]/12 years	26	18	44	59	41	4 = 16 %	4 = 22 %	18 %
≧ 3 years....	23	10	33	70	30	10 = 43 %	4 = 40 %	42 %
Total	103	59	162	64	36	18 = 17 %	9 = 15 %	27 = 17 %

The problem as to whether asthmatic bronchitis is a forerunner or not of asthma bronchiale has been considered in the present work. A questionaire form was sent out in 1951 to 185 children who in 1940—1945 were admitted to the Children's Hospital on Fuglebakken and in the children's ward in Sundby Hospital with the diagnosis of asthmatic bronchitis. The criteria for diagnosis have been those mentioned above; all the children had prolonged expiration, rales or rhonchi. An enquiry was also made as to whether the children had had regular attacks of asthma since they left the hospital.

There were 4 children who had died. Two, according to informations received, died from pneumonia, the eldest one was 2 $^1/_2$ years old.

TABLE 3

The relation between pure asthmatic bronchitis and asthmatic bronchitis as a result of or in association with another infection in the respiratory organs, and the prognosis of these 2 groups with reference to the later development of asthma bronchiale; observation period 6—11 years.

Age on admission with asthmatic bronch.	Total	Pure asthmatic bronch.	Number of cases developing asthma bronch. later	Asthmatic bronch. as an associated phenomenon	Number of cases developing asthma bronch.
0—11 months	85	65 = 76 %	4 = 6 %	20 = 24 %	1 = 5 %
1—2 $^{11}/_{12}$ years	44	31 = 71 %	8 = 25 %	13 = 29 %	0
≧ 3 years	33	29 = 87 %	13 = 43 %	4 = 13 %	1(= 25 %)

The distribution of asthma among girls and boys and the prognosis for the individual sex are shown in table 2; in calculating the percentage, the patients who died and the patients from whom no forms were received have been omitted.

Table 2 shows that $^2/_3$ are boys and $^1/_3$ girls in all the four age groups. It is remarkable, that the same distribution of asthma bronchiale is found in both sexes (3, 8). Furthermore it can be seen from table 2, that the prognosis with reference to the development of asthma bronchiale later is the same in girls and boys, who at some time in their lives have had asthmatic bronchitis; and also that the later this form of bronchitis appears, the greater the risk of the later development of asthma bronchiale. It can be seen that asthmatic bronchitis is more frequently found in children less than one year old.

On the basis of the figures in table 2 there is no distinction between boys and girls when considering the following, and also when 0—5 months and 6—11 months are combined.

Frequently one will see an "asthmatic" reaction in children in association with an infection of the respiratory organs other than bronchitis, e.g. pneumonia. The question arises whether this is important for prognosis, when one considers the later development of asthma bronchiale, whether the patients' asthmatic bronchitis was "pure" (i.e. that no other contemporary infection of the respiratory organs was revealed at the examination), or if it was combined with other infections in the respiratory organs e.g. pneumonia. Exclusion of a pneumonia has been made mainly by the stethoscope + clinical judgment. The result of the analysis can be seen in table 3.

It is shown in table 3, that the number of children in the group 0—11 months, who later developed asthma bronchiale, is so small, that it is impossible to draw any conclusions with regard to prognosis in the 2 forms of asth-

matic bronchitis in this age group. It has become apparent that in the 2 groups 1—2 $^{11}/_{12}$ years and ≧3 years asthmatic bronchitis as a consequence of other infections present in the respiratory organs has a considerably better prognosis than *pure* asthmatic bronchitis. In this way 21 cases out of 60 in the "pure asthmatic bronchitis" group have developed asthma bronchiale, as compared with 1 case out of 17 where asthmatic bronchitis was a result of associated respiratory infections. To sum up it seems that the "asthmatic reaction" as a result of welldefined, localized infections in the respiratory organs (e.g. pneumonia) is nearly always nonspecific; and the later a patient has a pure asthmatic bronchitis the greater is the risk of a specific-allergic reaction and thus a forerunner of asthma bronchiale. This might be due to the fact that at later examination ages varied in the 3 age groups; one will find in any case a rising frequency of asthma bronchiale with increasing age up to forty years (3) or sixty years (5). In order to find out whether the age at onset of asthmatic bronchitis is important for prognosis, as shown in table 3, it will be necessary to consider the age at later examination in the 3 age groups used, as shown in table 4.

From table 4 it can be seen that the difference is so slight in the average ages at the later examination of the groups 0—11 months and 1—2 $^{11}/_{12}$ years (8.3 years versus 10 years) that it is of no value in explaining the differences in prognosis (6 % asthma bronchiale in the one group, as compared with 25 % in the other). Consequently one can conclude from table 4, that a pure asthmatic bronchitis in a child less than 1 year old has a better prognosis than in a child more than one year old. This comparison of prognosis cannot be utilised in the age groups 1—2 $^{11}/_{12}$ years and ≧3 years old in table 4, owing to the large difference in average ages (9.8 years versus 14.1 years). One has tried to improve this by leaving out patients in the oldest age groups who, at the time of the later examination were older than 11 and 13 years respectively. In doing so one realized that the average age at the later examination in the accepted age groups becomes almost identical, so that a comparison of the groups is permissible, as is carried out in table 4.

From table 4 it can be seen, that the difference in prognosis between the group 0—11 months and the two other groups is not due to the difference in average age at the time of the later examination. Furthermore it can be seen that may be there is a real difference in the prognosis between the groups 1—2 $^{11}/_{12}$ years and ≧3 years (26 % asthma bronchiale against 41 %). The prognosis in the group of asthmatic bronchitis ≧3 years old is more serious, than for any of the two younger age groups (within the first 11 years). To sum up, one can conclude from table 4 that pure asthmatic bronchitis in children less than one year old rarely leads to asthma bronchiale (6 % of all the cases). In children with pure asthmatic bronchitis

TABLE 4

Comparison between the prognosis for pure asthmatic bronchitis in the 3 age groups when the average age at the later examination is almost identical in the groups.

Age on admission with asthmatic bronch.	≧ 6 yrs and ≦ 11 yrs old at questionaire examination. In all	Average age at the later exam. Years	Percentage development of asthma bronch. %
0—11 months	65	8.3	6
1—2 $^{11}/_{12}$ years	24	9.8	25
≧ 3 yrs. (average: 4 yrs.)	4	9.3	(25)
	≧ 7 yrs and ≦ 13 yrs at later examination		
1—2 $^{11}/_{12}$ years	31	10.0	26
≧ 3 yrs. (average: 4,1 yrs.)	12	11.8	41
	≧ 9 yrs and ≦ 19 yrs at later examination		
≧ 3 yrs. (average: 5.3 yrs.)	29	14.1	43

School-Children in Copenhagen, aged 7—14 years, suffer. from asthma bronchiale: 0.8 % [11]

at the age 1—2 $^{11}/_{12}$ years asthma bronchiale will appear after 11 years in 25 % of the cases, and in children ≧3 years with pure asthmatic bronchitis, asthma will appear in 43 % after 11 years. In children less than one year old asthmatic bronchitis is therefore comparatively mild whilst this is not the case with pure asthmatic bronchitis in children more than 1 year old.

The frequency of asthma bronchiale amongst school children in Copenhagen between 7—14 years is barely 1 % (11); in children who have had pure asthmatic bronchitis it is 6—43 %, as shown above. There is consequently a greater risk of the later development of asthma bronchiale in any child with a pure asthmatic bronchitis, than in a child who has not suffered from this complaint.

From table 5 it appears that the familial tendency is identical in the 3 age groups (the difference between the group 0—11 months, and two other age groups i.e. 33 % as compared with 50 % is not significant), as $^1/_3$—$^1/_2$ of the children with pure asthmatic bronchitis are allergically disposed. At the same time it is shown (unfortunately figures are small) that the prognosis for asthmatic bronchitis becomes worse with age in the group with

TABLE 5

The prognostic importance of allergic disposals in pure asthmatic bronchitis; observation period 6—11 years.

Age on admission with asthmatic bronch.	Number questioned about allerg. disposition	Allergic dispositions found	Subsequent asthma bronchiale	Allerg. dispos. denied	Later asthma bronchiale
0—11 months	24	8 = 33 %	1 = 12 %	16 = 67 %	2 = 12 %
1—2 $^{11}/_{12}$ years	19	9 = 50 %	3 = 33 %	10 = 50 %	3 = 30 %
≧ 3 years	18	10 = 55 %	7 = 70 %	8 = 45 %	2 = 25 %

an allergic tendency, whilst it is only slightly worse in the nonallergic group; (the average age at the later examination of the two groups among children ≧3 years old is 14.6 and 15 years respectively). It is remarkable that the allergic disposition in children with pure asthmatic bronchitis is the same as asthma bronchiale i.e. 50 % (table 3).

From table 2—5 one can make the following conclusion: If one presupposes that a constitutional predisposition is necessary for an "asthmatic" reaction to occur in a child with bronchitis before the development of "real asthma" then this "preparedness" will reveal itself especially in children less than 1 year old (table 2) and more especially in the allergically disposed (table 5). The distribution of this predisposition between boys and girls (table 2) is the same as in asthma bronchiale (2 : 1). Children who have had an asthmatic bronchitis will in subsequent years suffer more often from asthma bronchiale than children without this constitutional characteristic, whether the children are allergically disposed or not. 10 %—70 % will have asthma bronchiale as compared with less than 1 % of normal children of the same age (table 5). In the group ≧3 years old in the allergically disposed with this preparedness the prognosis for their asthmatic bronchitis seems to be specially poor (table 5).

The importance of recurrent catarrhs in the prognosis of pure asthmatic bronchitis cases is shown in table 6. By recurrent catarrhs is meant the presence of infection in the respiratory tract at least one month before admission to hospital for asthmatic bronchitis.

From table 6 it can be seen that recurrent catarrhs are especially characteristic in the group ≧3 years old. It is shown also that in pure asthmatic bronchitis in children less than 1 year old, recurrent catarrhs are without any prognostic importance when considering the subsequent development of asthma bronchiale. In the age group 1—2 $^{11}/_{12}$ years it is not certain whether recurrent catarrhs make the prognosis worse; whereas this seems to be the

TABLE 6

The prognostic importance of recurrent catarrhs in cases of pure asthmatic bronchitis; observation period 6—11 years.

Age on admission with asthmatic bronchitis		Total	Subsequent asthma bronchiale
0—11 months	+ recurrent catarrhs	19	2 = 10 %
	÷ » »	46	2 = 5 %
1—2 $^{11}/_{12}$ years	+ recurrent catarrhs	16	5 = 31 %
	÷ » »	15	3 = 20 %
≧ 3 years (average: 5.2)	+ recurrent catarrhs	24	12 = 50 % (average age: 14.7 yr)
≧ 3 years (average: 7)	÷ » »	5	1 = 20 % (» » : 14.6 yr)

case for children ≧3 years. One concludes from this that in children with pure asthmatic bronchitis combined with recurrent catarrhs, that the symptoms are often due to specific-allergical mucous membrane reactions.

It seems peculiar that there is no connection between the allergic disposition and recurrent catarrhs; especially in the case of children less than 3 years old. The material is so small that one cannot draw any conclusions with regard to prognosis when one considers the allergic disposition and recurrent catarrhs. However it should be mentioned that in the groups ≧3 years old there were 7 out of 9 patients with the abovementioned combination, who had asthma bronchiale within 6—11 years.

The prognostic importance of eosinophilia in a pure asthmatic bronchitis is analysed. Eosinophilia (≧400 eosinophil cells per cmm) seems to be of prognostic importance; the figures however, are too small for any significant conclusions to be drawn. It is remarkable that amongst 10 children over 1 year old with eosinophilia 7 had asthma bronchiale after 6—11 years, whilst from the proportional figures for children without eosinophilia i.e. 8 children, only 1 case subsequently developed asthma bronchiale.

On admission body temperature ≧38° or <38° C is without any prognostic importance in all 3 age groups with pure asthmatic bronchitis. It is seen that it is especially in the age group 0—11 months that the patients react with an increase of temperature.

The material does not allow any conclusions to be drawn as to the ultimate importance of allergic skin diseases; in only 5 cases is skin disease mentioned in the case history. None of these patients suffered from asthma bronchiale later.

FLENSBORG *et al.* (9) have shown in children that the treatment of a supposed bacterial-allergic conditioned asthma bronchiale by continual vac-

cination with bacterial vaccines is favourable. Accordingly one might consider it advisable to carry out the same treatment with cases of asthmatic bronchitis. The treatment of pure asthmatic bronchitis with bacterial vaccines is not likely to be indicated in children less than 1 year because less than 10 per cent will develop bronchial asthma. Among children 1—2 $^{11}/_{12}$ years who have pure asthmatic bronchitis about 30 % will develop asthma bronchiale, and it seems therefore that it is right to institute vaccine treatment for this age group, even if $^{2}/_{3}$rds of the patients should recover without treatment. For children $\geqq 3$ years old with pure asthmatic bronchitis without any allergic disposition the same holds good, because 30 % will subsequently develop asthma bronchiale. There is an obvious indication for vaccine treatment if there is an allergic disposition present, because 70 % will develop asthma bronchiale.

When one examines the bacterial vaccine treatment of pure asthmatic bronchitis and its preventative value against the subsequent development of asthma bronchiale the abovementioned factors must all be taken into consideration i.e., age, allergic predisposition, recurrent catarrhs and eosinophilia.

Summary

One hundred and eighty five children with asthmatic bronchitis admitted to hospital during 1940—1945, were reviewed with an extensive questionaire in 1951, to see if asthma bronchiale had subsequently developed. One hundred and sixty six replies were received. The prognosis for asthmatic bronchitis as a result of an infection of the respiratory organs (e.g. pneumonia with prolonged expiration), is better than the prognosis for "pure" asthmatic bronchitis, and the prognosis is the same for both sexes. The older the child the more serious is the prognosis, especially among the allergically disposed; it is also worse among the nonallergically disposed than among children who have never had asthmatic bronchitis. It is not of any prognostic importance if the asthmatic bronchitis is associated with a temperature $\geqq 38°$ C on admission or not.

Less than 10 per cent of children with pure asthmatic bronchitis, who are less than 1 year old will develop asthma bronchiale. In children of 1—2 $^{11}/_{12}$ years and $\geqq 3$ years without any allergic disposition, 30 per cent will develop asthma bronchiale. In children $\geqq 3$ years old and with the allergic disposition, 70 per cent will develop asthma bronchiale. Vaccine treatment seems to be indicated in the last two groups.

Bronchite asthmatique chez les enfants. Pronostic de 162 cas examinés après 6—11 ans.

185 enfants atteints de bronchite asthmatique ont été admis a l'hopital de 1940 à 1945, et ont été revus en 1951 lors d'un examen poussé, afin de savoir si un asthme bronchique s'était développé. Le pronostic d'une bronchite asthmatique, résultant d'une infection des organes respiratoires (p. ex. pneumonie avec expiration plus longue) est meilleur que le pronostic d'une bronchite asthmatique «pure» et il est

le même dans les deux sexes. Plus vieux est l'enfant, plus sérieux est le pronostic spécialement parmi les prédisposés à l'allergie. Il est aussi pire parmi ceux qui ne sont pas prédisposés à l'allergie que parmi les enfants qui n'ont jamais eu de bronchite asthmatique. Il n'y a aucune importance pronostic si la bronchite asthmatique est associée avec une température de 38° lors de l'admission ou non. Moins de 10 pour cent des enfants atteints de bronchite asthmatique pure et agés de moins d'un an, aurons un asthme bronchial. Chez les enfants de 1—2 $^{11}/_{12}$ ans et $\geqq 3$ ans sans prédisposition allergique, 30 % aurons un asthme bronchique, chez les enfants de $\geqq 3$ ans avec prédisposition allergique, 70 % aurons un asthme bronchique. Le traitement vaccinal semble être indiqué dans ces deux derniers groupes.

Asthmatische Bronchitis bei Kindern. Prognose bei 162 Fällen, die 6—11 Jahre beobachtet wurden.

1940—1945 waren 185 Kinder mit der Diagnose „asthmatische Bronchitis" in das Kinderhospital Fuglebakken und an der Kinderabteilung des Sundby-Hospitals aufgenommen worden. 1951 wurden diesen Patienten Fragebogen zugesandt, um festzustellen, ob sich bei diesen Kindern ein Asthma bronchiale entwickelt habe. 166 Antworten gingen ein. Es hat sich gezeigt, dass die Prognose von asthmatischer Bronchitis als Begleitphänomen anderer Infektionen des Respirationstraktus (z. B. Pneumonie mit verlängerter Exspiration) besser ist als die Prognose der „echten" asthmatischen Bronchitis. Die Prognose ist für beide Geschlechter gleich, wenn auch das Leiden bei Knaben häufiger auftritt. Je älter das Kind mit der Asthmabronchitis ist, umso ernster ist die Prognose, besonders bei allergisch Disponierten scheint eine starke Verschlimmerung einzutreten. Hinsichtlich der Entwicklung eines Asthma bronchiale ist die Prognose gerade unter den nicht allergisch Disponierten schlechter, als bei Kindern, die nie eine asthmatische Bronchitis hatten. Es ist von keinerlei prognostischen Bedeutung, ob die asthmatische Bronchitis mit Fieber um oder über 38° C bei der Aufnahme einhergeht. Wenn man versucht asthmatische Bronchitis mit Bakterienvaccinen zu behandeln, muss berücksichtigt werden, dass bei Kindern unter 1 Jahr keine Indikation besteht, weil weniger als 10 % ein Asthma bronchiale entwickeln. Von den Kindern zwischen 1—2 $^{11}/_{12}$ Jahren und $\geqq 3$ Jahren mit echter Asthmabronchitis (und ohne jede allergische Disposition) entwickeln ca 30 % ein Asthma bronchiale; in diesen Fällen scheint eine Vaccinetherapie indiziert. Bei Kindern $\geqq 3$ Jahren mit allergischer Veranlagung entsteht bei ca 70 % ein Asthma bronchiale und hier ist die Behandlung absolut indiziert.

Bronquitis asmática en los niños. Pronóstico en 162 casos observados en 6—11 años.

Sobre 185 casos de niños con bronquitis asmática que habían estado hospitalizados durante el período 1940—1945 y a los que se envió un extenso cuestionario en 1951 para ver si subsiguientemente se había desarrollado un asma bronquial 166 respondieron a la encuesta. El pronóstico para las bronquitis asmáticas resultantes de una infección de los órganos respiratorios (como por ejemplo neumonia con expiración prolongada) es mejor que el pronóstico para las bronquitis asmáticas »puras», siendo igual el pronóstico para los dos sexos. Cuanto mayor es el niño mas serio el pronóstico especialmente entre aquellos con disposición alérgica. Es también peor entre los no predispuestos alérgicamente cuando estos niños no han tenido nunca bronquitis asmática. No es de ninguna importancia pronóstica el que en el momento de la admisión tengan o no temperatura = 38°. Menos del 10 % de los niños

con bronquitis asmática pura los cuales son menores de un año desarrollan posteriormente un asma bronquial. En los niños de 1—2 $^{11}/_{12}$ años y $\geqq$ 3 años sin una predisposición alérgica el 30 % desarrollarán un asma bronquial. Y en los niños $\geq$ de 3 años de edad con predisposición alérgica el 70 % desarrollan un asma bronquial. El empleo de tratamiento con vacuna parece estar indicado en los dos últimos grupos.

References

1. Baagøe, K. H.: Asthma; Nomenclature-definition-pre-asthmatic state. Acta allergol. *1:* 197: 1948.
2. —— Asthma, særligt hos børn. Thesis, København 1926.
3. Bray, C. W.: Recent Advances in Allergy. London 1937.
4. Brennemann: Brennemann's Practice of Pediatrics. II, 48: 4, 1946.
5. Clausen, O.: Asthma i Norge. Nord. med. *37:* 525: 1948.
6. Cooke: Allergy in Theory and Practice. Philadelphia 1947.
7. Engel, Stefan: The Childs Lung. London 1947.
8. Flensborg, E. W.: The prognosis for asthma in infancy after the nonspecific treatment hitherto applied. Acta pædiat.: *33:* 3. 1945—46.
9. Flensborg, E. W., Neerborg, G. & Samsøe-Jensen, T.: Om formentlig bakterielallergisk asthma hos børn og dens behandling. Ugesk. læger: *112:* 387: 1950.
10. Kobro, M. S.: Om behandling av asthma bronchiale og bronchitis asthmatica. Acta med. scandinav., suppl. CXXV, 1941.
11. Report from the Schools in Copenhagen 1949—50.

Received 18.2. 1952.

Börnehospitalet Martinsvej
Copenhagen F.

Acta Pædiatrica **42**: 97—112. March 1953

From the Children's Hospital University of Utrecht (Netherlands),
Head: Prof. Dr. A. ten Bokkel Huinink and
Central Institute for Nutrition Research T.N.O., Utrecht,
Head: Dr. M. van Eekelen.

Coeliac Disease

III. Excretion of Unsaturated and Saturated Fatty Acids by Patients with Coeliac Disease

by H. A. WEIJERS and J. H. van de KAMER

It is true that the coefficient of fat absorption, or the amount of fat in grams excreted per 24 hours, is a good standard for judging the severity of a steatorrhoea in the case of patients with coeliac disease, but it does not give sufficient insight into the *nature* of this symptom (WEIJERS—VAN DE KAMER). The differentiation of the faecal fat into saturated and unsaturated fatty acids offers more prospects in this respect (VAN DE KAMER—WEIJERS).

Principle of the quantitative determination of saturated and unsaturated fatty acids in fat from the faeces.

When the total number of milliequivalents of fatty acids in faeces is known, it is possible, after determination of the iodine value, to calculate what portion of the fatty acids is unsaturated. Then with the help of the average molecular weight of the saturated and unsaturated fatty acids, it can be calculated how many mg of each are present in the faeces.

The separation and purification of the fatty acids, followed by the determination of the iodine value, takes place as follows.

An arbitrary quantity of faeces is boiled with ethanolic KOH; next, this alkaline liquid which contains 75 % ethanol is extracted twice with petroleum ether, thereby removing sterols and other substances possibly present, which contain double bonds and which are not of an acid nature. After acidification it is again extracted twice with petroleum ether, in this case from a medium which contains 60 % ethanol. This extract, containing all higher fatty acids, is purified by shaking with acidified ethanol of 25 %, whereby the lower fatty acids which, in the previous extraction from ethanol 60 %, had not yet remained in the lower layer, are practically entirely removed. Now a suitable portion of the petroleum ether extract is titrated with ethanolic alkali 0.1 N with thymol blue as indicator to the first change from yellow to green. After evaporation of the petroleum ether, the soap is taken up in a solution of $KBrO_3$-KBr in water and after addition of carbon tetrachloride and HCl, the amount of bromine bound is determined by back titration (modification of the method of WINKLER).

This differentiation was therefore applied in the following examination of children with steatorrhoea. Some typical results are summarized in figures 1, 2 and 3.

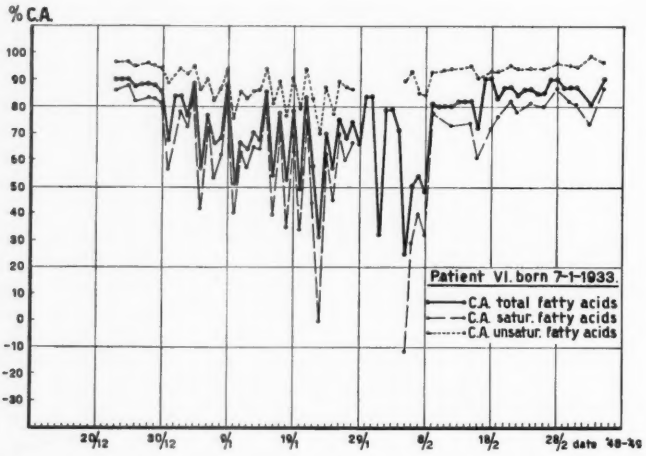

Fig. 1. Coefficient of absorption of fat and of the saturated and unsaturated fatty acids separately, on diets containing butter fat (daily determinations).

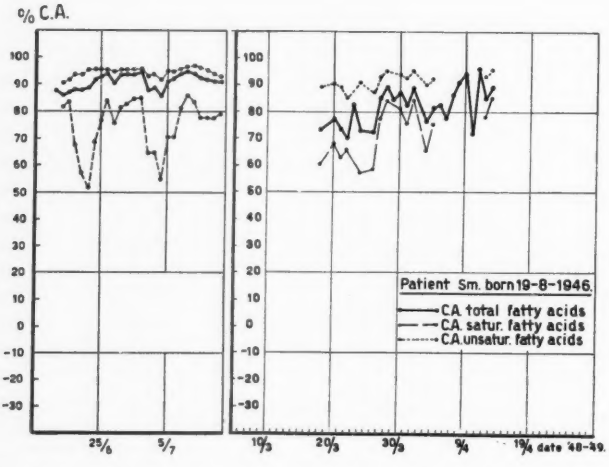

Fig. 2. Coefficient of absorption of fat and of the saturated and unsaturated fatty acids separately, on diets containing butter fat (daily determinations).

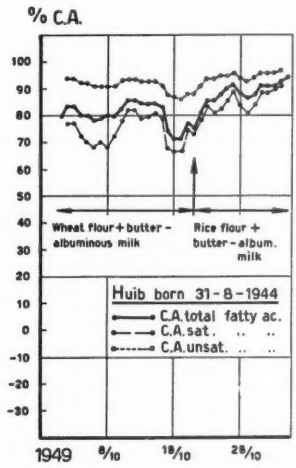

Fig. 3. Coefficient of absorption of fat and of the saturated and unsaturated fatty acids separately, on diets containing butter fat (daily determinations).

It is very noticeable that with all children in all stages of the diseases concerned, the C.A. of the unsaturated fatty acids ($C.A._{u.f.a}$) is significantly greater than the C.A. of the saturated fatty acids ($C.A._{s.f.a.}$). The same phenomenon had already been qualitatively observed (HOLT amongst others) in the case of *normal* persons and now this is clearly demonstrated with these patients.

The greater part of our observations was made in the case of children suffering from coeliac disease, thus a chronic disease. Because of this there is little chance of a spontaneous recovery during the period of testing. Moreover, it is easy to influence their C.A. by simple changes in the diet, by which it is possible to determine the $C.A._{u.f.a.}$ and the $C.A._{s.f.a.}$, as well by a high as by a low C.A.

The difference with the investigation of normal persons lies in the fact that in their case, the faecal fat consists of "endogenous" fat, while in patients with steatorrhoea, the faecal fat consists practically entirely of unabsorbed dietary fat and/or excretion fat.

Since we continually observed that more saturated fatty acids were excreted than unsaturated, and that the coefficient of absorption of the saturated fatty acids, e.g. in parenteral infections, declines first and strongest, it was obvious that the fat in the coeliac-patients' diet should contain little saturated fatty acids. Olive oil was chosen for this purpose. Since these patients were accustomed to having butter fat in the form of albuminous milk,

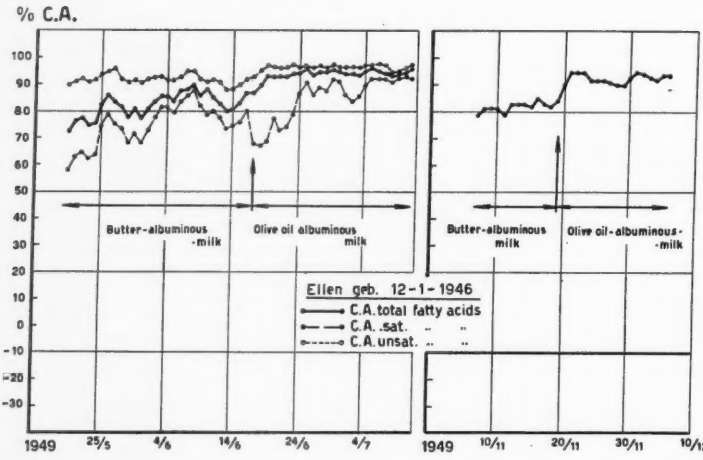

Fig. 4. Coefficients of fat absorption in a patient with coeliac disease on a diet containing butterfat (abt. 50 % of saturated fatty acids) and on the same diet after replacing the butterfat by olive oil (abt. 13 % of saturated fatty acids).

olive oil, instead of cream, was added to the fat free albuminous milk basis.[1] The *only* alteration made in the diet during the different investigation periods was the substitution of olive oil — albuminous milk for butteralbuminous milk (figure 4). As for the rest the experiments were carried out with diets which contained no wheat flour, but rice flour and potatoes.

It is evident that the olive oil immediately causes a significant rise in the C.A. of the collective fatty acids. This is in complete agreement with what was expected on the basis of figures 1, 2, 3. As few saturated fatty acids are administered with olive oil, the coefficient of absorption in this case is determined practically only by the size of the $C.A._{u.f.a.}$. When the coefficients of absorption of the unsaturated and saturated fatty acids are considered separately, it is noticeable that the $C.A._{u.f.a.}$ is slightly higher than when butter is used, in spite of the fact that a diet with olive oil contains almost twice as much unsaturated fatty acids!!

Clinically the patients showed a distinct improvement in the general condition, the humour was noticeably better, activity increased, the colour was better and indications of vegetative lability were less, while the stool was practically normal as regards odour, colour and consistency.

From these observations the conclusion, among others, can be drawn that a normal coefficient of absorption is not always a sign that the fat absorption

[1] Our thanks are due to N. V. Nutricia in Zoetermeer for the preparation and delivery of this product.

is undisturbed. We see, in fact (fig. 4), the C.A. of coeliac patients, given olive oil instead of butter fat, suddenly rising from 85 % to 95 %, the normal value. In spite of the fact that the steatorrhoea has disappeared, we may not conclude from this that the fat absorption is now also normal, for the C.A. declines at once when butter fat is again given.

Obviously the next step was to find out if there is also a difference in excretion between the various saturated fatty acids. In the case of higher saturated fatty acids, this was tentatively investigated by giving patients coconut oil-albuminous milk. Coconut fat contains, namely, besides 18 % myristic, 9 % palmitic and 2 % stearic acid, also about 40 % lauric acid. This is likewise a saturated fatty acid, quite comparable with palmitic and stearic acid as regards chemical composition, but containing only 12 C-atoms and having a considerably lower melting point namely 43° C. Furthermore coconut fat contains 7 % capric and 8 % caprylic acid.

The result of these experiments is shown in figures 5 and 6.

In spite of the fact that the quantity of saturated fatty acids in coconut fat is considerably greater than in butter fat (almost twice as great), it is evident that the coefficient of absorption of the collective fatty acids on a diet with coconut fat, is equal to or perhaps even a little greater than that on a diet of butter fat. If all saturated fatty acids were equally well (or equally badly!) digested, a smaller coefficient of absorption would be expected on a diet with coconut fat. From the fact that this is not the case, it follows that lauric acid (C_{12}) is assimilated better than the other higher saturated fatty acids (C_{14}, C_{16}, C_{18}).

The remarkable phenomenon that in this case, using coconut oil albuminous milk, the $C.A._{u.f.a.}$ is *lower* than the $C.A._{s.f.a.}$, does not signify that a great quantity of unsaturated fatty acids is excreted; it is only a consequence of the fact that coconut oil contains very little unsaturated fatty acids, so that the $C.A._{u.f.a.}$ is strongly influenced by the unsaturated fatty acids of the "endogenous" fat. Thus no conclusions may be drawn from this course of the $C.A._{u.f.a.}$ with regard to the digestion of the unsaturated fatty acids of the dietary fat.

Until now only patients on a *diet of rice* were considered in the investigation. However, as it is known (DICKE—WEIJERS—V.D. KAMER) that a diet containing wheat flour is the cause of a significant increase in fat excretion, while, moreover, the patient's condition deteriorates, the u.f.a. — s.f.a. excretion was then studied in coeliac-patients on a *diet with wheat flour*. The results are recorded in the figures 1 and 3 and in the following figures 7, 8.

It can be seen that the $C.A._{u.f.a.}$ is considerably higher than the $C.A._{s.f.a.}$ on a wheat-butter diet, as well as on one with wheat-olive oil, and also on the respective rice flour diets. The excretion of the u.f.a. is not increased, the

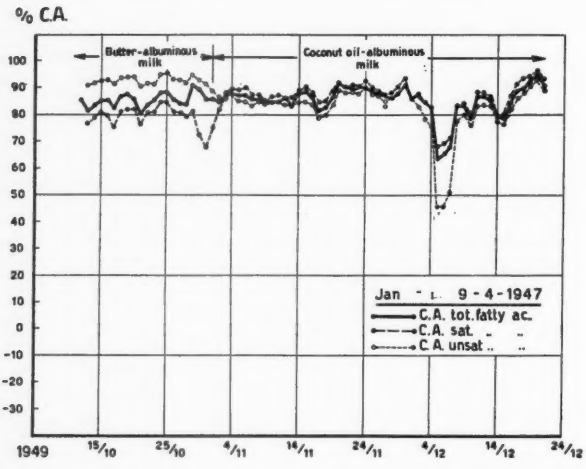

Fig. 5. Coefficients of fat absorption in a patient with coeliac disease on a diet containing butter fat and on the same diet after replacing the butter fat by coconut oil (about 50 % of lauric acid, C_{12}, and about 30 % of higher saturated fatty acids).

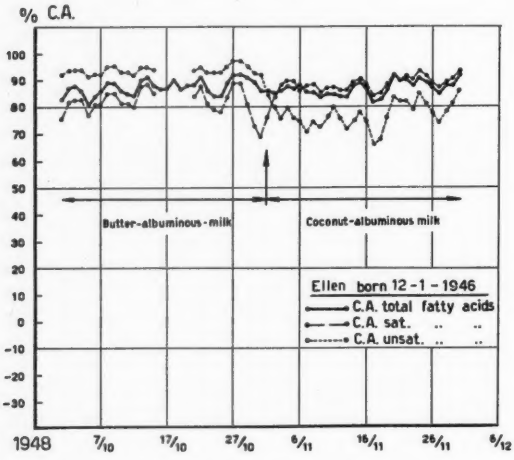

Fig. 6. Coefficients of fat absorption in a patient with coeliac disease on a diet containing butter fat and on the same diet after replacing the butter fat by coconut oil.

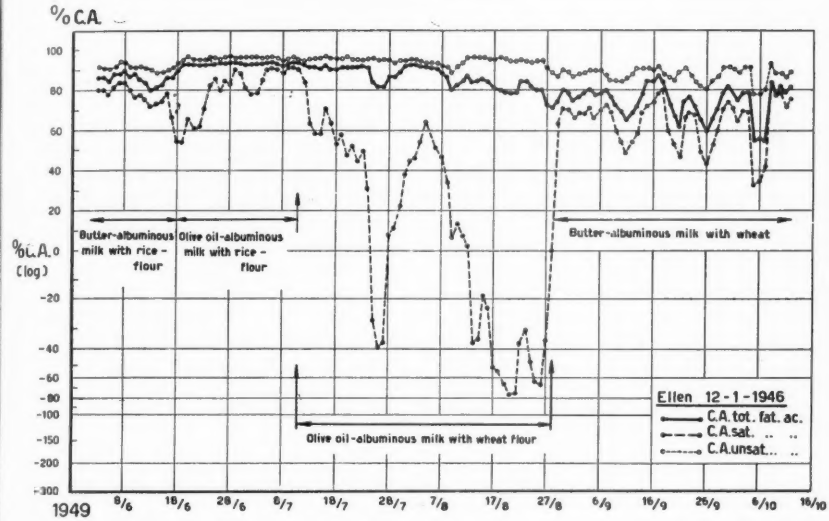

Fig. 7. The coefficients of absorption of the total fatty acids, the saturated and unsaturated fatty acids in a coeliac patient on a diet containing rice flour, later replaced by wheat flour and olive oil and butter fat respectively.

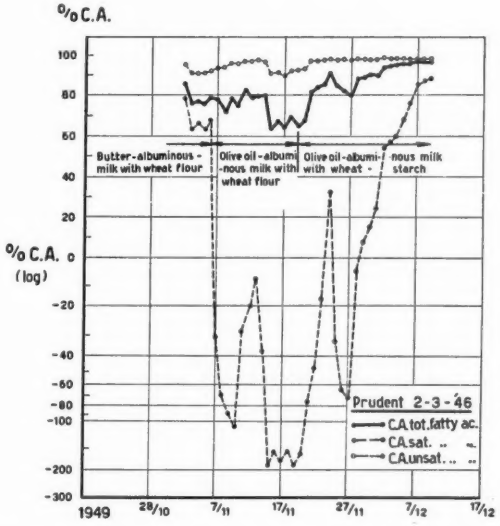

Fig. 8. Coefficients of absorption of the total fatty acids, the saturated and the unsaturated fatty acids of olive oil and butter in a patient with coeliac disease on a diet containing wheat flour.

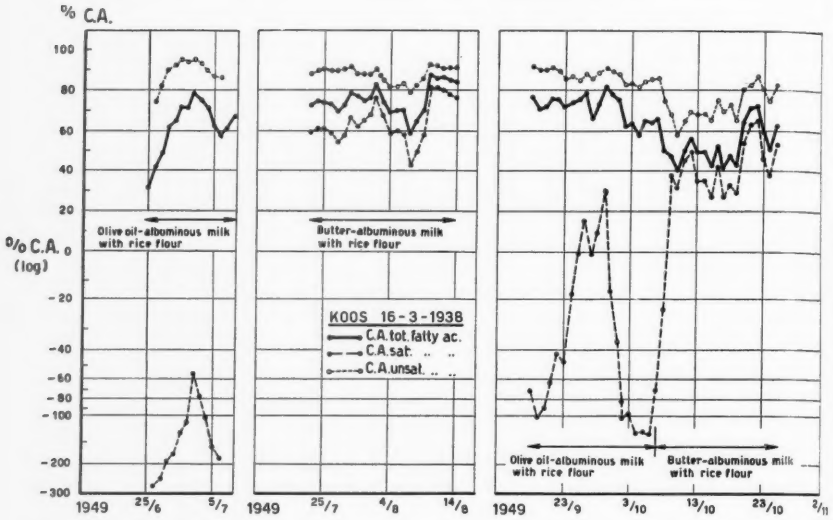

Fig. 9. The coefficients of absorption of the total fatty acids, the saturated and the unsaturated fatty acids in a patient with cystic fibrosis of the pancreas on a diet containing rice flour and olive oil and butterfat respectively.

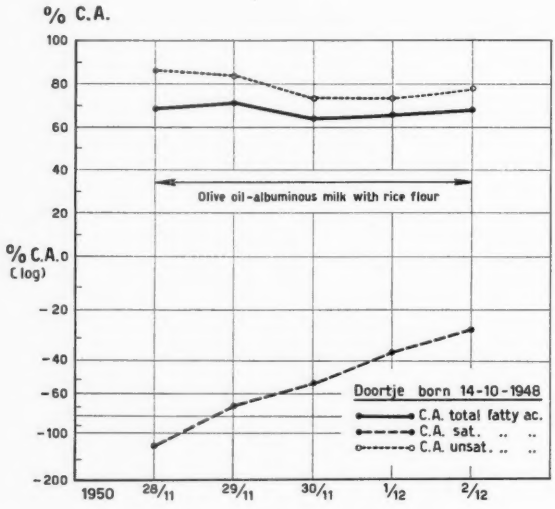

Fig. 10. Coefficients of absorption of the total fatty acids, the saturated and the unsaturated fatty acids in a child with cystic fibrosis of the pancreas on a diet containing olive oil and rice flour.

excretion of the s.f.a. is, however, considerably raised by the use of wheat flour. With the consumption of olive oil, even more saturated fatty acids are repeatedly excreted than absorbed, which therefore means a "*negative*" C.A.$_{s.f.a.}$ (fig. 7, 8).

In two cases of pancreatic fibrosis also, a negative C.A.$_{s.f.a.}$ was determined when the diet contained olive oil — albuminous milk. The remarkable difference with coeliac disease, however, was that this C.A.$_{s.f.a.}$ was found on a diet containing *rice flour* (fig. 9 and 10).

Since in the cases mentioned above, more saturated fatty acids are found in the faeces than are taken up with the food, it is impossible to speak of a coefficient of absorption, as this is negative. In order to make comparison possible between the results until now obtained, these "negative" values were, however, included in the graphs.

From the fact that more saturated fatty acids are excreted with the faeces than are taken up with the food, it follows that we are not dealing with a disturbed absorption, or at least not with that alone. As an explanation for this, we could for instance consider that intestine bacteria convert unsaturated fatty acids into saturated fatty acids. However, various arguments can be adduced in opposition to this.

In the first place the fat excretion on a (fat free) diet containing wheat flour was observed, while during 6 days 320 mg streptomycin was administered per/os.[1] It appeared that the fat excretion continued unchanged, in

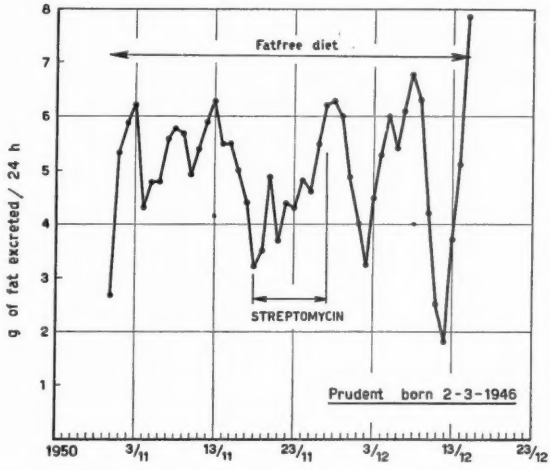

Fig. 11. Influence of streptomycin (320 mg daily orally) on the fat excretion of a coeliac patient on a *fat free* diet.

[1] Suggested by Dr. H. L. Barnett, New York.

TABLE I

Faecal colony counts

(Number of colonies/0.01 mg of faeces)

Date	E. coli commune	E. coli communi-or	E. coli neapolit.	E. coli acidilact.	Entero-cocci	Staphyloc. alb. nonh.	Spore-bearing bacilli and Lactobacilli	Staphyloc. aur. nonh.	Paracolob. escherich.	Streptomycin-hydrochloride 320 mg orally	g of faeces excreted per 24 hours
15/11	–	33	–	20	10	> 100	~	–	–	–	148
15/11	–	–	24	5	11	80	~	–	–	–	
17/11	13	–	–	16	157	–	–	–	–	–	146
18/11	–	–	–	1	26	–	20	–	–	+	178
21/11	3	–	–	–	–	–	–	–	–	+	139
22/11	1	–	–	–	18	–	> 100	–	–		79
22/11	–	–	–	–	432	–	> 100	–	–	+	
24/11	2	–	–	–	–	–	–	–	–	+	112
25/11	1	–	–	–	1	2	–	–	–	+	144
27/11	2	–	–	–	–	–	–	–	–		143
27/11	–	–	–	–	–	?	~	–	–	+	
28/11	–	–	–	–	–	3	–	–	–		296
28/11	–	–	–	–	–	~	–	~	–	–	
29/11	–	–	–	–	204	5	–	–	–	–	119
30/11	13	–	–	–	1600	6	–	–	–		145
30/11	22	–	–	1	150	–	–	–	1	–	
1/12	–	2	–	–	15	1	–	–	–	–	119

Influence of streptomycin (320 mg daily orally) on the bacteria in the faeces of a coeliac patient on a fat free diet.

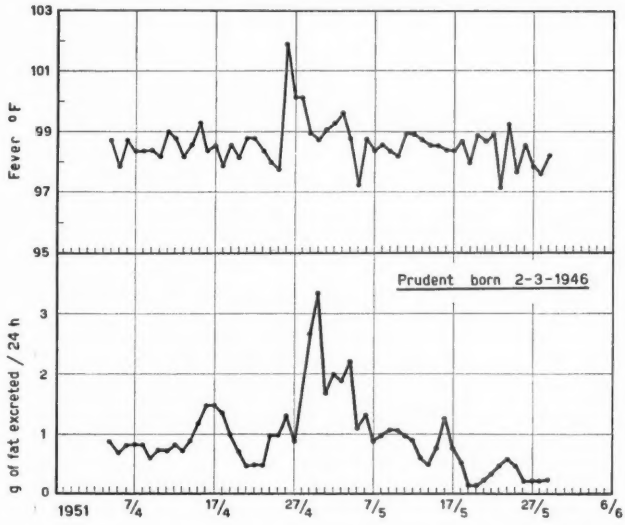

Fig. 12. Correlation of fever and fat excretion in a child with coeliac disease.

spite of the fact that after 2 or 3 days the quantity of bacteria in the faeces was reduced to nearly nought (see fig. 11 and table I).

In the second place an increase in the fat excretion, occurring during periods with fever without any change in the diet consumed, can hardly be interpreted as related to a change of the intestinal microflora.

The observations, recorded in the following figure, are of the more importance since the patient consumed a *fat free* diet.

In the third place it is highly improbable that the bacteria regularly occurring in the faeces — which on a fat free diet amounts to not more than 200 g per day — should contain 5—7 g fat. Since 200 g faeces, namely, correspond to about 40 g dry substance, and normally contains 10—15 g dry bacterial soma, the half of the dry bacterial soma ought to be fat. This is very unlikely, because the normal faecal microflora contain only about 5 % fat calculated with regard to dry substance. Whether *abnormal* liposynthetic micro-organisms may play a rôle in the fat-excretion observed in coeliac disease is under investigation.

Fourthly, very great periodical variations in the $C.A._{s.f.a.}$ can be seen in patients with pancreatic fibrosis (see fig. 9). This can hardly be ascribed to a change in the bacterial flora, as the diet, which contained olive oil — albuminous milk and rice-flour remained unchanged. True, a definite correlation was seen to exist between the general condition of the patient and the size of the absorption coefficient.

Thus the high excretion of higher saturated fatty acids cannot be explained on the basis of bacterial conversions. We are therefore inclined to seek the cause of this phenomenon in a fat *excretion*. That we are indeed concerned with a fat excretion in coeliac disease is seen when the coeliac-patients are given a *fat-free* diet. Following a diet containing butter-albuminous milk and amylum tritici, the patient Prudent was given a *fat free* diet consisting of skimmed milk powder, potatoes, vegetables, fruit and amylum tritici. After a while the amylum tritici in this diet was substituted by wheat flour (see figure 13).

And about two months later the wheat flour was replaced by rice-flour. Following the diet containing olive oil-albuminous milk and wheat flour the patient Ellen was given a fat free diet containing wheat flour. After a month the wheat flour was replaced by rice flour (see fig. 14).

It is plainly shown in figures 13 and 14 that these coeliac patients excrete large quantities of fat with the faeces without taking up fat. To look for the cause of this fat excretion in a disturbance of the intermediary fat digestion is obvious.

It is not necessary to suppose a fat excretion in the case of patients consuming a diet without wheat-flour; in these cases the steatorrhoea could be caused by a disturbance in the absorption. It is, however, very tempting to consider a disturbance in the intermediary fat digestion in these cases also.

An anatomical basis has indeed never been found in coeliac disease, from which an absorption disturbance could be explained; while also all enzymatic processes connected with fat-absorption follow a normal course. Moreover, hypotony, vegetative lability and disturbed psyche, the typical symptoms of coeliac disease, indicate a metabolic disorder much more than one of absorption.

It is also not necessary to accept an absorptive disturbance as an explanation for the flat chylomicron and vitamin A curve; they can proceed from a *retarded* absorption caused by hypotony of the intestine, or by rapid delivery of vitamin A by the blood to the different organs. In this connection consider also the retarded absorption of glucose, which is shown in a flat blood-sugar curve. The blood-sugar curve is normal when the tonus of intestine is raised by the administration of mecholyl (MAY—MCCREARY—BLACKFAN).

As no account was taken of excretion either in coeliac disease, or other diseases with steatorrhoea, it is very desirable to investigate if fat-excretion occurs in these diseases also (sprue, rachitis, t.b.c., lambliasis, icterus, etc.).

At the same time we refer to figure no. 6 part I, especially to the good C.A. with breast-feeding, in comparison with the frequently low C.A. with artificial feeding. In this case also an investigation must be made to find out whether we have to deal with a difference in absorption or in fat-excretion.

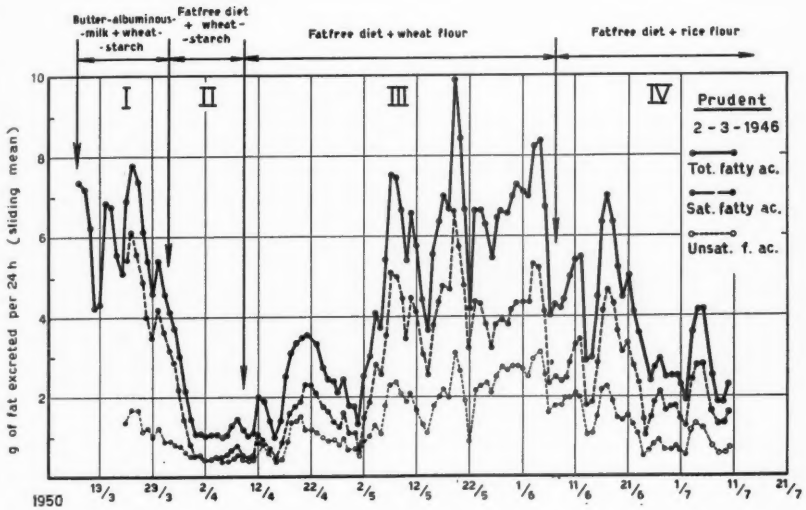

Fig. 13. Fat excretion (in g per 24 hours) of a coeliac patient on fat free diets containing wheat starch, wheat flour and rice flour respectively.

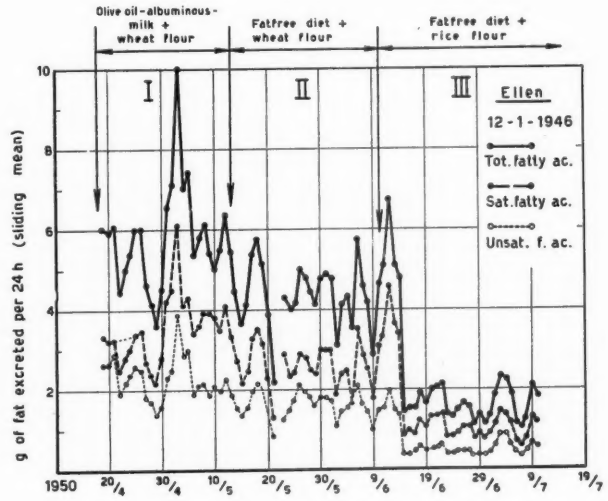

Fig. 14. Fat excretion in g per 24 hours of a coeliac patient on a fat free diet containing wheat flour and rice flour respectively.

Summary

Patients with coeliac disease always excrete more saturated than unsaturated fatty acids with the faeces. If the diet contains practically only unsaturated fatty acids in the form of olive oil, then the fat excretion is normal (C.A. = 95 %). If the diet contains wheat flour instead of rice flour, noticeably more saturated fatty acids are excreted, while the excretion of unsaturated fatty acids remains practically the same. That in this case we have not only to deal with a disturbed *fat absorption* is shown by the fact that with a diet of wheat flour + olive oil more saturated fatty acids are excreted than taken up with the diet. From this we can conclude that a *fat excretion* exists in the case of patients with coeliac disease who use wheat flour. This was confirmed by experiments whereby, on a fat free diet containing wheat flour, considerable quantities of fat were excreted with the faeces. Consequently it must be assumed that a disturbance in the intermediary digestion exists in coeliac disease.

Therefore it is very tempting to consider a disturbance in the intermediary fat digestion also in the case of coeliac patients consuming a diet without wheat flour.

It was evident that in pancreatic fibrosis also, the steatorrhoea in some measure is caused by fat excretion. In connexion with this, it is important to take into account the possibility of fat excretion, due to a disturbed intermediary fat digestion, being present in other diseases with steatorrhoea: sprue, rachitis, tuberculosis, lambliasis, icterus, etc.

Maladie coeliaque. III. Excrétion des acides gras saturés et non saturés chez les malades atteints de maladie coeliaque.

Les malades atteints de maladie coeliaque excrêtent toujours plus d'acides saturés que d'acides non saturés dans leurs faeces. Si le régime ne contient pratiquement que des acides gras non saturés sous forme d'huile d'olive, l'excrétion des graisses est normale (absorption = 95 %). Si le régime contient de la farine de blé au lieu de farine de riz, les acides gras saturés sont remarquablement plus excrétés, tandis que l'excrétion des acides gras non saturés reste pratiquement la méme. Dans ce cas nous n'avons pas seulement un trouble de *l'absorption* des graisses ce qui est montré par le fait que avec un régime de farine de blé + huile d'olive les acides gras saturés sont excrétés en plus grande quantité que l'on en a absorbé avec le régime. Nous pouvons conclure de cela que *l'excrétion* de la graisse existe dans le cas des malades atteints de maladie coeliaque qui mangent de la farine de blé. Ceci a été confirmé par des expériences par lesquelles avec un régime libre contenant de la farine de blé, des quantités considérables de graisses sont excrétés par les faeces. Il s'en suit que l'on doit penser que ce trouble de la digestion intermédiaire existe dans la maladie coeliaque. C'est pourquoi il est trés tentant de considérer ce trouble de la digestion intermédiaire des graisses aussi dans le cas de malades atteints de maladie coeliaque suivant un régime sans farine de blé. Il est évident que dans la fibrose du pancréas aussi, la stéatorrhée dans quelques mesures est causée par l'excrétion des graisses. En connexion avec ceci, il est important de tenir compte de la possibilité d'excrétion graisseuse, due à un trouble du métabolisme intermédiaire des graisses dans d'autres maladies avec stéatorrhée: sprue, rachitisme, tuberculose, lambliase, ictère etc. . . .

Coeliakie. III. Ausscheidung gesättigter und ungesättigter Fettsäuren bei Coeliakie-Patienten.

Patienten mit Coeliakie scheiden immer mehr gesättigte als ungesättigte Fettsäuren im Stuhl aus. Wenn die Diät praktisch nur ungesättigte Fettsäuren in Form von Olivenöl enthält, dann ist die Fettausscheidung normal (Retention = 95 %). Wenn die Diät Weizenmehl statt Reismehl enthält, werden deutlich mehr gesättigte Fettsäuren ausgeschieden, während die Ausscheidung ungesättigter Fettsäuren praktisch gleich bleibt. Dass wir es in diesem Fall nicht nur mit einer gestörten *Fettabsorption* zu tun haben, zeigt die Tatsache, dass mit einer Diät aus Weizenmehl und Olivenöl mehr gesättigte Fettsäuren ausgeschieden als aufgenommen werden. Daraus können wir schliessen, dass eine *Fettausscheidung* bei Coeliakiepatienten, die Weizenmehl zu sich nehmen, besteht. Dies wurde bestätigt durch Versuche, bei denen während einer fettfreien Diät mit Weizenmehl, beträchtliche Mengen von Fett im Stuhl ausgeschieden wurden. Konsequenterweise muss daraus eine Störung im Intermediärstoffwechsel bei Coeliakie abgeleitet werden. Deshalb liegt es nahe, auch bei den nicht mit Weizenmehl ernährten Coeliakiepatienten eine Störung des Intermediärstoffwechsels anzunehmen. Zweifelsohne ist die Steatorrhoe auch bei Pankreasfibrose in gewissem Umfang durch die Fettausscheidung verursacht. In Verbindung damit ist es wichtig, auch bei anderen Erkrankungen mit Störungen des Intermediärstoffwechsels die Fettausscheidung in Betracht zu ziehen, wie bei Sprue, Rachitis, Tuberkulose, Lambliasis, Icterus usw.

Enfermedad celíaca. III. Excreción de ácidos grasos no saturados y saturados en pacientes con enfermedad celíaca.

Los pacientes con enfermedad celíaca siempre eliminan por las heces una mayor cantidad de ácidos grasos saturados que de no saturados. Si la dieta contiene prácticamente solo ácidos grasos no saturados en forma de aceite de oliva entonces la excreción de grasa es normal (absorción = 95 %). Si la dieta contiene harina de trigo en vez de harina de arroz entonces se eliminan mayor cantidad de ácidos grasos saturados, mientras que la excreción de ácidos grasos no saturados permanece prácticamente igual. No hay solamente un trastorno de la *absorción grasa*, come es mostrado por el hecho que con la dieta de harina de trigo y aceite de oliva se eliminan mas ácidos grasos saturados que los que son administrados con la dieta. De ello puede deducirse que en los pacientes con enfermedad celíaca que reciben harina de trigo existe una *eliminación de grasa.* También se confirma de un modo experimental viendo que en los pacientes alimentados con una dieta libre de grasas pero que contiene harina de trigo se eliminan por las heces considerables cantidades de grasa . . . Consecuentemente debe decirse que existe en la enfermedad celíaca una alteración de la digestión intermediaria. Por ello es tentador el considerar pueda haber una alteración de la digestión intermediaria de las grasas también en el caso de los celíacos consumiendo una dieta sin harina de trigo. Es evidente que en la fibrosis pancreática la esteatorrea en la misma medida es causada por la excreción de grasa. En conexión con ello es importante tener en consideración la posibilidad de excreción grasa debida a alteración de la digestión grasa intermediaria que puede estar presente en otras enfermedades con esteatorrea como el esprue, raquitismo, tuberculosis, lambliasis, ictericia, etc.

Acknowledgement

The authors wish to thank Mr. J. G. Heyl, State Institute of Public Health, Utrecht, for carrying out the differential faecal colony counts reported in this study.

Addendum

When this article was in the press an Editorial appeared in the Lancet *262* (1952, Apr. 26) 857—858, entitled: "Coeliac Disease and Wheat"; in the same issue (pag. 836—842) an article by Ch. M. Anderson, A.C. Frazer, J. M. French, J. W. Gerrard, H. G. Sammons and J. M. Smellie, entitled "Coeliac Disease: Gastrointestinal studies and the effect of dietary wheat flour," confirming our results.

References

DICKE, W. K., H. A. WEIJERS and J. H. VAN DE KAMER, Coeliac disease. II. The presence in wheat of a factor having a deleterious effect in cases of coeliac disease. Acta Pædiat. 42: 34, 1953.

HOLT, L. E., A. M. COURTNEY and H. FALES, A study of the fat metabolism of infants and young children I, II, III. Am. J. Dis. Child. *17:* 241; 423, 1919; *18:* 107, 1919.

HOLT JR., L. E., H. CL. TIDWELL, C. M. KIRK, D. M. CROSS and S. NEALE, Studies in fat metabolism. I. Fat absorption in normal infants. J. Pediat. *6:* 427, 1935.

KAMER, J. H. VAN DE, Quantitative determination of the saturated and unsaturated higher fatty acids in fecal fat. Scand. J. clin. & lab. Invest. *5:* 30, 1953.

MAY, C. D., J. F. MCCREARY and K. D. BLACKFAN, Notes concerning the cause and treatment of celiac disease, J. Pediat. *21:* 289, 1942.

TIDWELL, H. C., L. E. HOLT JR, H. L. FARROW and S. NEALE, Studies in fat metabolism. II. Fat absorption in premature infants and twins. J. Pediat. *6:* 481, 1935.

WEIJERS, H. A., De vetresorptie van gezonde en zieke zuigelingen en kinderen in het bijzonder van coeliakiepatienten (Fat absorption in normal and abnormal infants and children with special reference to coeliac disease). Thesis, Utrecht 1950.

Received 1.4. 1952

Central Institute for Nutrition Research T.N.O., Utrecht. Netherlands.

Acta Pædiatrica **42**: 113—125. March 1953

From the Departments of Pediatrics, Karolinska Sjukhuset, Stockholm, Sweden and Vanderbilt University School of Medicine, Nashville, Tennessee.

Further Studies of Tuberculin Hemagglutination in Tuberculous Infection, Benign and Virulent[1]

by R. LAGERCRANTZ, J. C. PETERSON and J. LIND

In an earlier, and preliminary study (4), we have reported the results of hemagglutination tests using the MIDDLEBROOK-DUBOS (3) technique, as modified by SCOTT and SMITH (5), in a group of children with benign and virulent tuberculous infections. In this paper, we wish to discuss some additional findings and to comment on the results obtained in the previous study in relation to the increased data.

Test Reproducibility

Throughout these studies we have continued to run at least two samples of blood from previous tests as controls with each set of tests. As a result of this practice we have accumulated a number of double-determinations on a variety of serum samples. The only difference in the sera was a brief period of storage of 5° C. between the determinations. An examination of the results of these double-determinations, enables us to evaluate the reliability of the technique as practiced in our laboratory. For this comparison the titers were ranked according to logarithmic scale ranging from 0 through 9 according to whether the sample showed no demonstrable agglutinin or a titer as great as 1/512. The difference in titer log observed between first and second tests in 162 duplicates is shown in Table I.

TABLE 1

Logarithmic Differences in Titer Observed Between the 1st and 2nd Tests in 162 Duplicate Titrations Run at Different Test Times.

	−4	−3	−2	−1	0	+1	+2	+3	+4
Number	2	2	9	34	83	25	6	1	0
Per Cent	1.2	1.2	5.6	21.0	51.2	15.4	3.7	0.6	0

[1] These studies were supported by a grant from Svenska Nationalföreningen mot Tuberkulos. The Old tuberculin used in these studies was supplied by Lederle Laboratories, Pearl River, New York.

From this tabulation we can see that 88 % of the tests yielded the same titer or one step greater or less on the second test, 9.2 % of the tests showed changes of two steps plus or minus and 3 % of the tests showed changes greater than this degree.

There is a slightly greater tendency for the test to show a difference on the minus side than on the plus side on repetition. This might be interpreted as indicating that there is some loss in antibodies during storage. The tests are too few in number to attempt to correlate them with the storage period but some of the samples were stored for periods of several weeks between the first and the second test.

In a laboratory equipped for greater precision in carrying out these studies, a greater degree of reliability might be achieved. Certainly from the results of these observations one would not be able to attach very much significance to a rise of one or two steps in a titer of antibody in an individual under observation. On the other hand a change of several steps in repeated observations of an individual might be expected to occur only with some change in the infectious process, or the individual's response to it.

The Effect of Tuberculin Testing on Hemagglutination Titer

In our previous report on hemagglutination studies, the question of the effect of tuberculin testing on hemagglutination titer was raised. It was suggested in that study that increased titers of hemagglutinating antibodies might be excited by the repeated tuberculin tests required for ruling an individual tuberculin negative. In practice, this has consisted of a salve test (MERIOUX) followed in three days if negative by a Mantoux test, first with 0.1 of a mg and finally with 1.0 mg of tuberculin. The blood samples were drawn at the time the determination was deemed positive or three days after intradermal injection of a milligram of tuberculin. We have examined 76 individuals tested in this manner, some of whom were tuberculin negative and some of whom were tuberculin positive to one or another of the tuberculin tests.

Sixty-one of the 76 individuals showed the same titer on retesting, as they had shown before the tuberculin test. Thirteen showed titers one step higher and two showed a titer which was one step lower than the titer observed before tuberculin testing. These findings are summarized in Table II.

It is apparent that there may be a slight tendency to increase the titer following tuberculin testing but the levels of antibody increase observed are not significant.

TABLE 2

Logarithmic Changes in Agglutinin Titer
Following Tuberculin Testing, Three to Twelve Days After
The First Application of Tuberculin

Degree of change	−2	−1	0	+1	+2
Number	0	2	61	13	0
Per cent	0	2.6	80.2	17.1	0

BCG Vaccination

In our previous study we showed that among a group of infants who had received BCG vaccination at birth, and who were discharged after a relatively short period of time to their homes, where there was a presumably inactive case of tuberculosis, there was a rise in tuberculin hemagglutinating antibodies which usually appeared sometime during the second year of life. The question was raised as to whether this was a delayed response to the BCG vaccination or whether it was secondary to an additional stimulus. In the present study, we have examined another group of infants and young children who were BCG vaccinated at birth with observations at a period one to many months after their primary vaccination but who, during this time, had lived in a nontuberculous environment. Most of these individuals were from children's homes and thus had not been exposed to tuberculosis. In these children, as in the group previously studied and who, in the earliest months after vaccination were also free from tuberculous contact, there was no appreciable

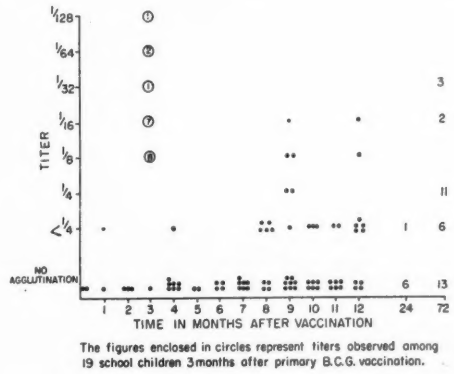

Fig. 1. Tuberculin Agglutinin Titers Observed Among Infants and Children Who Were Kept in a Tuberculosis Free Environment Following Their Vaccination with BCG.

TABLE 3

The Number and Per Cent of Individuals Showing Tuberculin Agglutinins Following BCG Vaccination at Birth According to Their Possible Contacts with Tuberculosis

Agglutinin Titer	Age							
	0—6 Mos.		6—23 Mos.		24 Mos. or more		Total	
	No.	%	No.	%	No.	%	No.	%
Individuals Living in a Tuberculous Environment After Vaccination								
1/64					4	9.1	4	6.5
1/32			1	6.2	2	4.5	3	4.9
1/16			1	6.2	2	4.5	3	4.9
1/8					2	4.5	2	3.3
1/4			7	43.8	24	54.5	31	50.8
< 1/4			1	6.2	6	13.6	7	11.5
No agglutination	1		6	37.5	4	9.1	11	18.0
Total	1		16	99.9	44	99.8	61	99.9
Individuals Living in a Nontuberculous Environment After Vaccination[1]								
1/64					3	6.8	3	1.5
1/32			1	1.2	2	4.5	3	1.5
1/16			1	1.2	3	6.8	4	2.0
1/8			3	3.5			3	1.5
1/4	3	4.3	2	2.4	13	29.5	18	9.1
< 1/4	3	4.3	17	20.0	8	18.2	28	14.1
No agglutination	63	91.3	61	71.8	15	34.1	139	70.2
Total	69	99.9	85	100.1	44	99.9	198	99.9

[1] Many of the individual tests among this group were run at the same time as the tests for those in the upper segment of the table.

rise in antibody during the first 7 months post vaccination. The distribution of the titers is shown in Figure 1. In the period beyond 7 months, 33 per cent of the observation showed low titers, 1/32 or less, and an additional 33 per cent showed traces of antibody, partial agglutination in dilutions of $^1/_4$.

Also shown in Figure 1 are the results of titrations run 3 months after BCG vaccination on 19 older, school children. In this age group, as will be reported more fully elsewhere, there is a relatively prompt post vaccinal rise in antibody. They also show even higher titers after a longer period of time (2).

In Table III we have combined the observations from the group of infants in the present studies with the group reported previously, who in the majority observations after 6 months, were from homes with possible tuberculous contact. This contrasts the findings among those who lived in nontuberculous

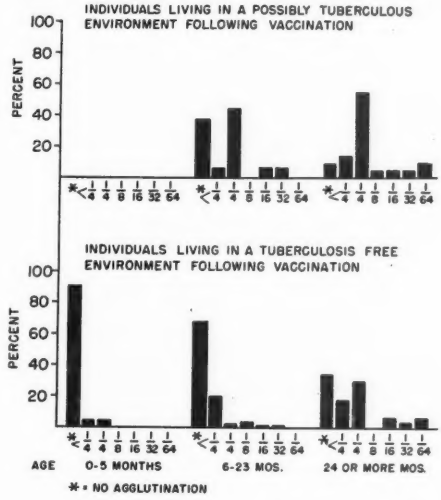

Fig. 2. Tuberculin Agglutinin Titers Following BCG Vaccination in the Neonatal Period, According to the Possible Subsequent Exposure of the Individual to Tuberculosis.

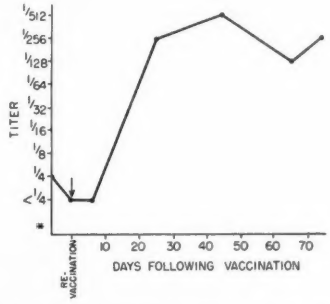

Fig. 3. Tuberculin Agglutinin Titers before and after BCG Revaccination.

environment after vaccination with those living in homes where some individual had or had had tuberculosis. The observations are shown graphically in Figure 2. From these one can see that there is an appreciable difference in the two groups with respect to the findings of moderate levels of antibody. And with respect to the finding of low levels of antibody, titers of $^1/_4$ and $<^1/_4$ there is a significant difference in the distributions. The individuals living in a tuberculous environment generally show higher levels of antibody than those not living in such an environment.

It is apparent from these studies that infants have a remarkable delay be-

fore they begin to show antibody after BCG vaccination. This must mean that the antigenic stimulus from this benign infection lasts over a long period of time after all clinical signs of its activity have ceased.

We have also been able to study the antibody response following revaccination to BCG in 16 individuals. A typical response is shown in Figure 3. Within a month this individual had shown a rise in titer from $< 1/4$ to 1/256, an increase of 5 steps in the test. Twelve of the 16 individuals showed a rise of at least 2 steps within the first month following revaccination.

Virulent Tuberculous Infection

In the previous study and in this study we have been able to accumulate data on 408 tests made during the course of primary tuberculous infection. In many instances these represent repeated tests on an individual under study.

The dynamics of the development of tuberculin agglutinin varies considerably from individual to individual, but they can be visualized best in the examination of serial tests run on the individual. In Figures 4 and 5 we

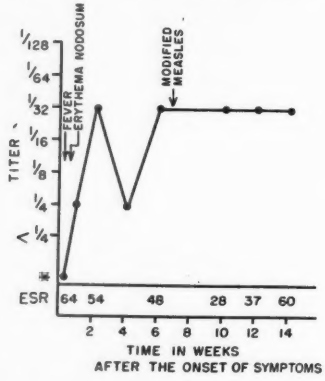

Fig. 4. Tuberculin agglutinin Response in a Case of Primary Tuberculosis.

Case Summary: E. J., a 5 year old girl who was tuberculin tested early in October 1951. because of repeated respiratory infections. The test was negative. On October 26th she was tired and ill. The following day she had a slight fever, 38° C and the next day developed erythema nodosum. When admitted to the hospital 2 days later her tuberculin test was positive with an abscence of tuberculin agglutinins. Roentgenograms showed an infiltration of the right lung with an enlarged hilar node. The ESR was 52. Gastric lavage yielded a positive guinea pig test for tubercle bacilli. A throat culture yielded B. hemolytic streptococci for which she was given penicillin. She was fever free after 10 days, began to gain weight and had some decrease in the sedimentation rate. During the 7th week she had modified measles without loss of tuberculin sensitivity or change in the agglutinin response. At discharge, 14 weeks after the onset, roentgenograms showed regression of infiltrative process.

Fig. 5. Tuberculin Agglutinin Response in a Case of Complicated Primary Tuberculosis.

Case Summary: Y. F., a 4 1/2 year old girl developed a sore throat followed in 2 days by erythema nodosum. The erythrocyte sedimentation rate was increased and gastric lavage yielded a positive guinea pig inoculation for tubercle bacilli. A month after the onset she had a low titer of agglutinins. The roentgenograms showed a typical primary complex. Course was afebrile after the first few weeks, except for temporary indispositions with intercurrent infections. Four months after the onset roentgenograms showed an increase in the pulmonary infiltration and bronchoscopy revealed an endobronchial infection. She was then treated with streptomycin and P.A.S. with subsequent improvement. Seven months after the onset new endobronchial infection, threated with antibiotics and local drainage. When discharged, 9 months after the onset, her condition was good.

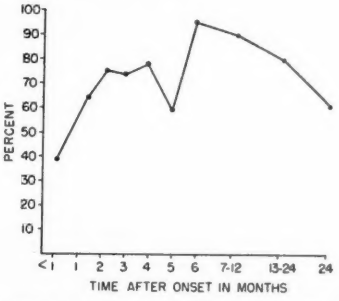

Fig. 6. The Percent of Individuals with Primary Tuberculosis Showing Tuberculin Agglutinin Titers Higher Than 1/8 at Various Times after Onset.

have summarized the course of the infection and the agglutinin responses in two fairly typical cases of primary tuberculosis.

The total variability of the response is better shown in an examination of the responses of a large group of individuals.

In Table IV is shown a summary study of a total of 313 observations[1]

[1] 408 observations were made but in Table IV we have included only the highest titer-value during each month in every case.

made on 174 patients during the course of their primary tuberculous infection. From the distribution of these figures it is apparent that antibody production is relatively low during the first 3 months of infection, that it increases slowly to reach a peak between 6 and 12 months after infection. A moderately high titer is observed in about 90 % of the individuals at this time. This falls off slowly during the succeeding months. In general, the individuals who have relatively benign infections show minimal increases in hemagglutination titers whereas those who have more serious or complicated infections show higher titers and the titers remain high for a longer period of time. The peak elevation of the titer remains high until after all symptoms have disappeared, declining slowly thereafter. These findings are shown graphically in Figure 6.

TABLE 4

Tuberculin Agglutinin Titers Observed at Various Periods After the Onset in Primary Tuberculosis

Degree of Agglutinin Response	Time After Onset in Months										
	<1	1	2	3	4	5	6	7—12	13—24	24	Total
≧ 1/8	10	30	29	26	25	11	16	49	25	6	227
< 1/8	16	17	10	10	8	8	1	6	6	4	86
Total	26	47	39	36	33	19	17	55	31	10	313
% ≧ 1/8	38	63	74	72	76	58	94	89	80	60	72

We have had an opportunity to follow only one case of miliary tuberculosis. This individual developed high titers of agglutinin, 1/128 to 1/512, which persisted for a long period of time, even after the blood sedimentation rate and the x-ray findings were normal.

Tertiary Tuberculosis

In a group of individuals with late tertiary manifestations of tuberculosis, primarily bone and joint tuberculosis, it was found that the great majority of them had high titers of agglutinin. Among the 77 cases observed all but one showed titers higher than $^1/_4$ and 62 % of them showed titers 1—32 or higher. These findings are summarized in Table V.

Normals and Individuals with Latent Tuberculosis

In latent tuberculous infection and in normal individuals as represented by a random sample of 100 Swedish blood donors, some of whom had been previously BCG vaccinated, some of whom had not received previous BCG vaccination and a number in whom this was indefinite but who had probably

TABLE 5

Tuberculin Agglutinin Titers Observed in Late Tuberculous Infections, Bone and Joint Tuberculosis.

Degree of Agglutinin Response	No.	%
>1/128	7	9
1/32—1/128	40	2
1/8 —1/16	26	34
<1/8	4	5
No agglutination	0	0
Total	77	100

not been BCG vaccinated, we observed titers ranging up through 1—64 (43 % of the individuals showed titers of at least $^1/_8$). All of these individuals can be assumed to have had reasonably good health. The distribution of the observed titers seen in the blood donor group is shown in Table VI.

TABLE 6

Tuberculin Agglutinin Titers Observed Among 100 Healthy Blood Donors.

Titers	BCG Vaccinated		Not BCG Vaccinated		Indeterminate But probably not BCG vaccinated		Total
	No.	%	No.	%	No.	%	No.
1/64			1	3			1
1/32	4	9	3	9			7
1/16	11	24	5	16	4	17	20
1/8	7	15	5	16	3	13	15
1/4	1	2	0		0		1
<1/4	17	38	15	47	13	56	45
No agglutination	5	11	3	9	3	13	11
Total	45	99	32	100	23	99	100

From these observations it is apparent that single low titers or unchanging titers of agglutinin can be of no diagnostic significance in a population where latent tuberculosis or experience with BCG is common.

Discussion

The specificity of the tuberculin agglutination reaction has been established to a point where it is no longer questioned. The value or exact significance of individual observations, however, is still a moot point. As a screen-

ing tool, the hemagglutination test falls into the same class as the tuberculin test, with an added disadvantage of being technically less readily applied. However, in patients with obscure infections the demonstration of rising titers of agglutinins would be of diagnostic significance and the protracted absence of agglutinins would be of value in excluding a possible tuberculous etiology. For example, in obscure bone and joint disease, the absence of agglutinins would strongly suggest a nontuberculous etiology and high titers might be acceptable as confirmatory evidence of a tuberculous etiology.

The test can be duplicated with a reasonably satisfactory degree of reliability, approximately equivalent in this respect to other agglutination tests.

The additional data presented here concerning the late appearance of agglutinin in infants following BCG vaccination, when they have been kept in an environment free of tuberculous contact, can surely be interpreted as indicating that the antigenic stimulus from this benign tuberculous infection extends over a long period of time, possibly as long as two years. This is in agreement with the anatomical finding of living BCG in the lymph nodes, for long periods of time (CALMETTE, GUERIN and BIRAUD).

The hemagglutinin response in infants following BCG vaccination is not only delayed, as compared with older children, but the titers achived are also relatively low as compared with those obtained following vaccination of school children (3). This type of immunologic response in infants has been demonstrated in several other immunizing procedures.

It is interesting to speculate on the observed differences in response following BCG vaccination between those maintained in an environment free of tuberculosis and those where tuberculosis may have been present.[1] The differences would, of course, suggest that these infants had had a superinfection, presumably with virulent organisms, from their environment. These children, who have been closely followed, have had no clinical signs of any additional tuberculous infection. On the other hand, the difference might result from other factors in the environment affecting the child's general health. The home may provide, even with its possible tuberculosis exposure, a more optimal milieu.

The late appearance of the antibody response in infants also indicated that the hemagglutinating antibody is of little or no real significance in protecting the individual from virulent tuberculous infection. It is well established that the protection from BCG vaccination is effective in infants long before the slowly rising agglutinin appears. This would, of course, agree with the generally accepted thesis that immunity in tuberculosis is largely the result

[1] As stated above there is a difference in the frequency of titer-values of $<1/4$ and $1/4$ between the two groups. As the hemagglutination test is not specific in these low titer-values, one cannot draw definite conclusions from these differences.

of the capacity of tissues to respond rather than being a function of a humoral mechanism.

Our studies also suggest that there is a good recall mechanism in the development of antibody following BCG vaccination. The curves obtained in the revaccinated individuals generally showing a greater elevation of antibody which appeared at an accelerated rate of development as compared with individuals following primary vaccination. So far we have not been able to accumulate any appreciable amount of data with respect to the anamnestic antibody response following dissemination or reactivation of a latent primary infection. We have observed examples where there was a delay in response as well as some in which there was a prompt recall. One would assume that most infections, not overwhelming, would stimulate a recall type of reaction. This recall mechanism is not sensitive enough to affect the results of agglutinin studies following tuberculin testing when the studies are carried out within a period of 2 weeks after the initial tuberculin test.

In primary tuberculosis our studies have enabled us to extend our observations, and where one is able to follow several tests at relatively short intervals, smoth curves of agglutinin appear, usually during the 3rd month of illness, but occasionally as late as the 5th month. All of our more recent patients showed rises in titer. We have been unable to observe an exact correlation between the type of infection and the patient reaction with the agglutinin response, but, in general, more severe and more complicated cases do produce greater and more persistent elevations of antibody and minimal and moderate infections produce low levels of antibody. The individual variation is very great.

The elevated titers persist after the symptoms of the infection and clinical findings, such as increased sedimentation rates, have disappeared. Another point of interest was the chance observation in four individuals of antibody titers before and after a superimposed attack of measles. The measles did not result in a change in the agglutinin comparable to the tuberculin anergy often observed in such instances.

Summary

Additional data on the tuberculin hemagglutination test in various types of tuberculous infection have been presented. The reproducibility of the test has been examined by running duplicates at different times. BCG vaccination in the neo-natal period evokes a agglutinin response only after a relatively long period of time, whether or not the child has additional exposure to tuberculosis. Infants having such exposure develop higher titers, without having clinical evidence of any superinfection. Revaccination with BCG evokes an anamnestic type of antibody response. The anamnestic response is not activated sufficiently or promptly enough by tuberculin testing to affect hemagglutinin studies within 2 weeks after the first tuberculin test. — 163

patients with primary tuberculosis have been followed with repeated tests. Most show an elevated titer; the rise in titer sometimes occurring as late as 3—5 months after the onset of disease. There is no definite correlation between the clinical picture and the titer-value. Cases of tertiary tuberculosis, as exemplified by bone and joint tuberculosis, generally show moderate to high elevations of tuberculin agglutinin, which should be useful in the differential diagnosis of obscure cases.

Etudes compleméntaires sur l'hémoagglutination au cours de l'infection tuberculeuse bénigne et virulente.

Les auteurs ont donné des résultats supplémentaires sur le test de l'agglutination tuberculinique au cours de différents types cliniques d'infection tuberculeuse. La possibilité de reproduction du test a été examinée par comparaisons à différents moments. La vaccination par le B. C. G., dans la période néonatale, entraine une réponse hémaglutinique seulement après une période relativement longue que l'enfant ait ou non été exposé à une surinfection tuberculeuse. — Les enfants qui entrent dans ce dernier cas (restant exposés) ont un titre plus élevé que les autres même s'il n'y a pas de signes cliniques évidents de surinfection. La revaccination par le B. C. G. donne un type de rappelle de la réponse des anticorps. Cette réponse n'est pas influencée suffisamment et rapidement par le test à la tuberculine pour entrainer des variations de l'agglutination dans les 2 semaines qui suivent le 1:er test de tuberculine. Les cas de tuberculose tertiaire comme la tuberculose ostéoarticulaire montrent généralement une évolution modérée ou marquée des agglutinines qui pourrait être utile dans le diagnostic différentiel des cas obscurs.

Weitere Studien über die Tuberkulin-Hämagglutination bei benignen und virulenten tuberkulösen Infektionen.

Zusätzliche Daten über den Tuberkulin-Hämagglutinationstest bei verschiedenen Formen tuberkulöser Infektionen werden wiedergegeben. Die Reproduzierbarkeit des Testes wurde durch laufende Doppelbestimmungen zu verschiedenen Zeiten geprüft. BCG-Impfung in der Neugeborenenperiode ruft nur nach einem relativ langen Zeitabschnitt eine Hämagglutinationsreaktion hervor, gleichgültig ob das Kind zusätzlich tuberkulös exponiert ist oder nicht. BCG-Revaccination verursacht einen anamnestischen Typ von Antikörperreaktion. Die anamnestische Antwort wird durch Tuberkulintestung nicht genügend oder prompt genug aktiviert, um die Agglutinationstiter innerhalb von 2 Wochen nach der ersten Tuberkulintestung beeinflussen zu können. Fälle von tertiärer Tuberkulose, beispielsweise Knochen- und Gelenktuberkulose, zeigen gewöhnlich eine mässige bis starke Erhöhung der Tuberkulin-Hämagglutination, eine Tatsache, die wichtig für die Differentialdiagnose unklarer Fälle sein kann.

Más estudios sobre la hemoaglutinación en la infección tuberculosa, benigna y virulenta.

Se presentan datos adicionales al test de la hemoaglutinación tuberculina en varios tipos de infección tuberculosa. La reproducibilidad del test ha sido controlado por continuas pruebas en distintos tiempos. La vacunación con el BCG en el período neonatal produce una respuesta hemoaglutinica solamente después de un período de tiempo relativamente largo, tanto si el niño está adicionalmente expuesto a la tuberculosis o no. Los niños expuestos a una tal infección producen títulos más altos sin presentar ninguna prueba clínica de superinfección. La revacunación con el BCG

produce un tipo anamnéstico de respuesta de anticuerpos. La respuesta anamnéstica no es lo suficiente o lo bastante rapidamente activada por el test de la tuberculine para afectar estudios sobre hemoaglutinación dentro de 2 semanas después del primer test tuberculino. Casos de tuberculosis terciaria, puestos como ejemplo por tuberculosis ósea y articular, muestran generalmente elevaciones de moderadas a altas de hemoaglutinina tuberculina que podrían ser útiles en el diagnóstico diferencial de casos obscuros.

Bibliography

1. Calmette A., Guérin, C. and Biraud Y. Vaccination antituberculeuse par le BCG. Comité d'Hygiène de la Société des Nations, l'Institut Pasteur de Paris, 1928.
2. Enell, H. and Lagercrantz, R. To be published in Acta Pædiat. *42*, 1953.
3. Middlebrook, G. and Dubos, R. J., Specific serum agglutination of erythrocytes sensitized with extracts of tubercle bacilli. J. Exper. Med. *88:* 521, 1948.
4. Peterson, J. G., Lagercrantz, R., Rollof, S. I. and Lind, J., Tuberculin hemagglutination studies in active tuberculous infections, benign and virulent. Acta Pædiat. *41:* 57, 1952.
5. Scott, N. B. and Smith, D. T., A simple modification of the Middlebrook-Dubos hemagglutination test for serum antibodies to products of tubercle bacilli. J. Lab. & Clin. Med. *35:* 303, 1950.

Received 15.4. 52.

Barnkliniken
Karolinska sjukhuset
Stockholm.

Acta Pædiatrica **42**: 126—129. March 1953

From the University Children's Clinic, Helsinki, Finland,
Chief: Professor Arvo Ylppö, M.D.

On Plasma Calcium in Cord Blood and in the Newborn

A Preliminary Report

by NIILO HALLMAN and IRJA SALMI

Studies on plasma calcium of the newborn are frequently encountered in the literature. Determinations have been performed so abundantly that CLEMENT SMITH, in his book "The Physiology of the Newborn Infant" is fully justified in asking "why so much effort has been expended upon the problem is a little curious, for there is quite good agreement in almost all the results." Investigations have been performed on both the cord blood and blood of the newborn, and as a common feature in all, it has been found that as early as on the first day of life, plasma calcium shows a marked decrease as compared to cord calcium (DENZER *et al.*, TODD *et al.* etc.). When studying umbilical blood, either blood "milked" from the cord or blood taken from the umbilical vein has been used. In this work we have performed studies on the calcium content in arterial and venous cord blood, and our researches throw light on the question why plasma calcium of the newborn is lower than cord calcium.

Method

The blood was withdrawn with a syringe direct from the umbilical artery and vein before severing the cord. Heparin was used to prevent coagulation. The blood specimen of the mother was taken either just before or immediately after delivery. The infant's sample was withdrawn from the deep jugular vein 1 to 3 days after birth. The samples were centrifuged for separation of the plasma, never later than within one hour.

Determinations of the calcium content were performed with the help of GROAK's micromethod, invariably making three parallel determinations, with their average taken as the result. The difference between these parallel determinations was ± 3 %. More exact figures will be published later.

Results

The appended table presents the results obtained from the cord blood entering the infant (vena umbilicalis) and leaving the infant (arteria umbilicalis), the infant's venous blood 1 to 3 days after birth and the venous blood of the mother. Placental blood entering the foetus regularly contains more

TABLE I

Calcium content in arterial and venous cord blood, in venous blood of the infant and in venous blood of the mother.

Case	Vena umbilicalis mg/100 ml	Arteria umbilicalis mg/100 ml	Vena jugularis profunda[1] mg/100 ml	Venous blood of the mother mg/100 ml
1	10.5	9.0	9.2	10.2
2	11.6	10.4	11.2	10.4
3	11.4	10.6	10.7	10.5
4	12.6	11.3	11.0	10.0
5	13.0	12.3	11.2	11.7
6	12.8	12.0	11.5	10.1
7	11.7	11.3	11.1	9.8
8	14.0	11.7	10.3	11.7
9	11.1	10.8	10.5	9.1
10	12.2	11.4	11.6	9.9
11	11.5	11.1	11.5	9.3
12	11.3	10.2	10.8	10.3
13	11.1	10.3	9.6	9.3
14	12.0	11.2	11.2	8.8
15	11.8	10.5	10.8	10.5

[1] The blood was taken 1—3 days after delivery.

calcium than the blood which is brought back. The difference varies between 0.3—2.3 mg/100 ml. The blood of the umbilical vein as well generally shows a higher calcium content than in the infant blood after birth, the difference being 0—3.7 mg/100 ml.

The plasma calcium content of the blood entering the placenta from the foetus falls approximately into the same category as that of the infant's plasma calcium on the days following delivery. In 7 cases the infant's plasma calcium after delivery was lower (difference 0.1—1.1 mg/100 ml.), in 7 cases higher (difference 0.1—0.8 mg/100 ml), and in one it was equally high as in the blood brought back into the afterbirth from the foetus.

The plasma calcium of the mother was always unmistakably lower than the calcium content of the umbilical vein. In several cases it was also lower than the calcium in the umbilical artery. In the latter cases the difference was, however, not equally pronounced, and even the reverse was true in some instances.

Comment

The results obtained show that the blood entering the infant from the placenta always has a markedly higher calcium content than the blood which flows into the placenta. This is true for the moment of birth. Since the foetus

has a rapid growth, particularly during the last months of pregnancy, this result was to be expected. As even the blood entering the placenta often has a calcium content surpassing the plasma calcium of the mother, this suggests an increased activity in placental function in order to satisfy the requirement for calcium of the growing infant.

Among previous investigators e.g. BAKWIN attempted to explain the fall in the plasma calcium of the infant as compared to calcium of the cord and occurring immediately during the first hours of life, by insufficiency of the parathyroidal function. Our studies furnish evidence that the high calcium content of the cord blood found by earlier investigators is due to the circumstance that no consideration has been given to the different direction of the blood flowing through the cord. Either venous blood alone has been studied (e.g. NOHLEN) or the blood oozing from the cord, which in fact is mainly venous blood as well. It is known that the amount of blood in the infant depends to a large measure on how early the cord was ligatured. The amount of the blood increases if the cord is not ligatured immediately after delivery. It is evident that the umbilical arteries tend to close up of themselves, and in any case, do so before the veins. This circumstance explains why, when making a cross section of the cord, one gets more venous blood.

One of us is continuing researches along these lines, to throw additional light on the matter reported by us.

Summary

A study is made of calcium contents in arterial and venous cord blood, the plasma calcium of the newborn (aged 1 to 3 days) and of the mother in 15 cases. The blood entering the infant from the afterbirth invariably contains more (0.3—2.3 mg/100 ml) calcium than the blood brought back from the infant. The calcium contents of the blood entering the placenta and of the infant's blood after birth are approximately on the same level, and the values are frequently higher than for the calcium of the mother. The findings of earlier investigators that the elevation of the cord calcium is high as compared to calcium of the infant, is mainly due to the circumstance that no separate consideration has been given to umbilical artery and umbilical vein.

Étude sur le calcium plasmatique contenu dans le sang du cordon et chez le nouveau-né.

Cette étude porte sur le calcium contenu dans le sang artériel et veineux du cordon, le calcium plasmatique du nouveau-né (entre 1 et 3 jours) et chez la mére dans 15 cas. Le sang arrivant à l'enfant après la naissance contient invariablement plus de calcium que le sang sortant de l'enfant (0,3—2,3 mg/100 ml). Le taux de calcium sanguin entrant dans le placenta et le taux de calcium sanguin de l'enfant après la naissance sont sensiblement les mêmes et ces valeurs sont fréquemment plus élevée que le taux de calcium chez la mère. Les découvertes des chercheurs précédents disant que le taux de calcium du cordon est élevé si on le compare à celui de l'enfant sont certainement dues au fait qu'on n'avait pas pris en considération de faire des études séparées du sang de l'artère ombilicale et de la veine ombilicale.

Über Plasmakalzium im Nabelschnurblut und bei Neugeborenen.

In 15 Fällen wurden Untersuchungen über den Kalziumgehalt im arteriellen und venösen Nabelschnurblut, das Plasmakalzium bei Neugeborenen (1.—3. Lebenstag) und der Mutter gemacht. Das in das Kind eintretende Blut enthält konstant mehr (0,3—2,3 mg/100 ccm) Kalzium, als das aus dem kindlichen Organismus zurückkommende Blut. Der Kalziumgehalt des Plazentablutes beim Eintritt liegt mit dem des kindlichen Blutes nach der Geburt etwa auf der gleichen Höhe, die Werte liegen hier häufig sogar höher als bei der Mutter. Die Befunde früherer Untersuchungen über die höheren Kalziumwerte im Nabelschnurblut im Vergleich zu den Kalziumwerten der Kinder sind durch die Tatsache, dass keine getrennten Untersuchungen in der Nabelarterie und Nabelvene durchgeführt wurden, zustandegekommen.

Sobre el calcio plasmático en la sangre del cordon y en el recién nacido.

Se hace un estudio de el contenido en calcio de la sangre arterial y venosa del cordon umbilical, del calcio plásmatico en el recién nacido (de edad de 1 a 3 días) y en las madres en 15 casos. La sangre entrando al niño después del nacimiento invariablemente contiene mas calcio (0,3—2,3 mg/100 c.c.) que la sangre de retorno del niño. El contenido calcico de la sangre que entra a la placenta y de la sangre del niño tras el parto son aproximadamente de un mismo nivel y los valores son frecuentemente mas elevados que los de calcio de la madre. Los hallazgos de los primeros investigadores sobre que el calcio de la sangre del cordón es mas elevado cuando se compara a la calcemia del niño era debido a la circunstancia que no se había tomado en consideración el separar si la determinación era hecha de la sangre de la arteria o de la vena umbilical.

References

Bakwin, H.: Pathogenesis of Tetany of the New-Born. Am. J. Dis. Child., *54:* 1211, 1937.

Denzer, B. S., Reiner, M. and Weiner, S. B.: Serum Calcium in the Newborn. Am. J. Dis. Child., *57:* 809, 1939.

Nohlen, A.: Über den Serumkalkgehalt des Blutes Neugeborener und ihrer Mütter. Ztschr. Kinderh., *42:* 60, 1926.

Smith, C. A.: The Physiology of the Newborn Infant. Springfield, Ill. USA., 1946.

Todd, W. R., Chuinard, E. G. and Wood, M. T.: Blood Calcium and Phosphorus in the Newborn. Am. J. Dis. Child., *57:* 1278, 1939.

Received 16.4. 1952

Barnkliniken
Stenbäcksgatan 11
Helsinki. Finland

Acta Pædiatrica **42**: 130—146. March 1953

From the Pediatric Department of Aarhus University Clinics at Aarhus Kommunehospital (Chief: Professor BENT ANDERSEN, M.D.), and the Medical Department of Aarhus Amtssygehus (Chief: Professor AAGE TH. JACOBSEN, M.D.).

On Psychogenic Obesity in Children II[1]

by NIELS JUEL-NIELSEN

This paper is based on a re-examination of 61 obese children (viz. 36 girls and 25 boys) aged from 2—14 years. The patients have been in hospital during the years 1940—48, and were reexamined during the year 1949.

The re-examinations were made through interviews with the patients and their parents, chiefly the mothers, who were summoned to Aarhus Amtssygehus. On the same occasion the patients were measured again for weight and height. A more direct estimation of the surroundings,—their social, economic, habitational, and psychological structure,—took place during one or several visits to the homes of the patients. For further illustration I have sought information in case-records on brothers, sisters, parents, or other relatives who have been admitted to one of the hospitals in the city of Aarhus or the county. Finally, in a great number of cases I have also applied to school authorities, social institutions, and in some cases to the Psychological School Board in Aarhus and the psychiatric clinics there.

The whole material of information has been checked, and often augmented with interviews with the G.P. who originally referred the patient to hospital for obesity.

The methods of investigation and particularly the procedure of the interviews with parents have been copied as closely as possible on the principles and lines of approach that BRUCH employed. All patients were in hospital for examination or treatment for obesity. The clinical picture in each case was one of definite obesity, often very marked. I have not considered it necessary to make any selection or to limit the material regarding the degree of overweight. Hence, in the first place I have been able to ignore such problems as otherwise present themselves when the degree of overweight (calculated on age and height) is taken as a criterion for the state of obesity. Principally this is the case regarding the choice of modern standard tables of geographical-national applicability; also when it comes to drawing a more or less arbitrary line between obesity and normality. If, as it is clinically customary, we determine the limits on a 15 % degree of overweight, then the result of a selection from a normal population will be groups that are numerically dominated by slight, and perhaps clinically and therapeutically insignificant, cases of obesity, whereas comparatively few very fat children will be included. It is my impression that parents of children with slight obesity rarely send for the doctor for that reason, at any rate they will often decline sending the children to hospital. If, on the other hand, we set the margin of overweight very high, hoping to gather a group of very fat children from among

[1] The introduction and first paper appeared in Acta Pædiatrica vol. 41: 577, 1952 and vol. 42: 8, 1953.

a normal population, then the population will have to be very great, or we shall not manage to find a suitable number of patients. In this connection I think it is safe to say that fifty-four of the children in my material can be regarded as representative of the fattest children that lived in the city and county of Aarhus (total population: about 180,000 inhabitants) within the above mentioned age periods. The remaining seven children, all of them unusually obese, had come for a specialist examination and treatment in Aarhus hospitals from various parts of the province of Jutland (Aarhus being the principal city not only of the county, but of the whole province as well).

According to the standard tables by NYBØLLE (1933)—most commonly used in Denmark, though hardly up to date—50 children (82 %) out of the 61 patients were found to be of more than 40 % overweight, and of these 16 (26 %) were of more than 70 % overweight; these figures only aim at giving a rough idea about the composition of the material regarding the degree of obesity.

As said above it was a clinical impression that the material is mainly made up of distinctly obese children, and when I stress this fact, it is not only because of the comparison with BRUCH's groups, which are dominated by clear and extreme cases of obesity; but also (vide below) because I think it may prove of importance for a demonstration of the existence of psychogenic mechanisms, when children develop obesity.

While the patients were in hospital, they have all been routinely examined for possible endocrine or other metabolic disturbances. Apart from a general somatic examination and clinical estimation, ophthalmoscopy; determination of basal metabolism; x-rayed skull, sella turcica, and carpus; in some cases glucose tolerance tests; examinations of serum cholesterol and excretion of hormones in urine have been performed. There was nothing in any of the 61 patients to support definitely the acceptance of a specific 'endogenous' aetiology. It should be noticed that among forty patients with specially x-rayed sella turcica, this showed considerably divergent measures in eight cases, in seven of which they were smaller than normal for the age. Weight and height on admission to hospital have been registered, but I have not in this paper scrutinized these purely somatic questions with regard to a special estimation of the interaction between height and weight; neither have I included the prognosis for obesity in childhood. The boys in my material that displayed the typical feminine localisation of obesity I have ranked with the rest of the patients; there was nothing in them that could justify a certain statement of veritable hypogenitalism or belated puberty.

The primary aim and purpose of my work has been to investigate the existence and importance of psychogenic mechanisms and causative relations with regard to onset, development, and maintenance of obesity in childhood, with particular reference to BRUCH's research and theory. According to her report, particularly as to the method of investigation, it should be reasonable to expect that the conditions described by her would be of such frequency and significance as to make it relatively easy to prove and reveal similar conditions, if her procedure was followed using Danish material, without resort to deep-probing psychological methods. However, it is hardly possible to estimate with any finality to what extent we can subsequently look upon the social and psychological constellations as recurrent and repre-

sentative characteristics for the surroundings of obese Danish children, until we have compared these phenomena with similar observations in a comparable material of non-obese Danish children. BRUCH has not produced for comparison a control series, but notifies that she wants one which will be applicable to the conditions in the U.S.A. As this present paper was limited by a time factor—it has not been possible to make collateral inquiries into Danish control material. To procure absolutely sufficient and relevant social and psychological data will presumably call for years of intensive teamvork and research based on very large groups of children. Thus the task is virtually limited to investigating whether the family constellations and psychogenic mechanisms assumed by BRUCH are demonstrable at all in Danish children, and—if so—with what frequency?

I have analysed the material in two ways. *In the first place*, through a correlation of all the social, psychological data and characteristics in connection with a rough general estimation of the material. I have made a comparison with the external structure (social, economic, family, matrimonial, psychological) which in BRUCH's opinion distinguishes the surroundings of obese children.

In the second place,—and this has been my chief concern—I have in each separate obesity case attempted to estimate the importance that emotional disturbances could have on this particular obesity picture. I have found it but little expedient to treat my material statistically, particularly as to the separate criteria and data. However, often numerical arrangements have been applied to materials of this size and nature, they can hardly be of any value as long as we are without great and exhaustively investigated materials where the occurrence and frequency of the said conditions have been treated and estimated statistically. Hence, the figures that will be found below have no other purpose than to make a rough comparison with BRUCHS' figures; they have not been furnished with any isolated statistical value, on the whole I do not think that the two materials are statistically comparable.

In the *analysis of the social, economic, and habitational conditions* of my material the family frame appears to differ considerably from BRUCH's material in this respect. Her representative selection, consisting of 40 children, is characterised by a definite homogeneity, seeing that they are all outpatients, the great majority coming from Jewish immigrant families living in New York. This all implies a specific social and psychological condition. My own series is less homogeneous, it is fairly representative of a rough cut through the social pyramid of a Danish provincial population. Arranged according to parent's professional position, the children belong in the following categories: 1) Working-class: 28, 2) Independent country people: 9, 3) Small civil servants, shop-keepers: 18, 4) Independent business-people: 4,

5) Intellectuals etc.: 4. More than three fourths of the patients lived in Aarhus or in small provincial towns in Jutland, the rest coming from the country proper. With the exception of two mothers all parents were of Danish nationality.

Economically only three of the homes could be called really badly off, in periods they were dependent on public relief. The homes had great difficulties in making both ends meet, and six had in periods been in the same precarious state. Fortytwo homes, i.e. more than two thirds of them all, were ordinary homes with stable means, and their social level as well as their culture interests were much higher than the corresponding cases in BRUCH's series. Nor were the housing conditions out of the ordinary. Only twelve families lived in small, bad, and crowded flats; most of the families lived in fairly good or excellent homes. The 61 families had a total of 160 children, on an average 2.6 per family, as compared to BRUCH's 2.1. As said before there is no available Danish control material fitted for estimating these and later figures.

BRUCH claims as a noteworthy fact the frequency of obese children among only children. My material did not corroborate this statement: 15 were only children, 20 were eldest born, 13 youngest, and 13 "in—between". For the sake of comparison I can say that the parents very often came of prolific families, but that may only be characteristic of the generation to which they belong. For some cases I can give exact information: in the families of 21 fathers there were a total of 96 children, on an average 4.7 children per family; the corresponding figures for 38 mothers being 188 and 4.8 Altogether 12 fathers and 26 mothers came of families with five children or more; only 2 fathers and 3 mothers were only children. Only in nine homes was the size of the family increased because the grandparents were living there; in all other cases the grandparents had died, or they lived in old age homes or in flats or houses of their own. Thus, in contradistinction to BRUCH's families, they cannot be said to have unduly encumbered the homes, though in many cases they may have influenced family life psychologically and economically.

As to parents' matrimony: 12 families must be nominated 'broken homes', 6 mothers being unmarried, 3 widows, and 3 separated. In 8 of these cases mother and patient lived with one or both parents of mother. The remaining 49 homes: in six cases matrimonial conditions were definitely bad with permanent quarrels and disagreement between parents. Two of these marriages were dissolved at the time of re-examination. Four marriages were in periods very discordant. The rest of the marriages, i.e. 33 homes or more than half the material, were seemingly of a neutral and non-committal character, nor did the parents seem to be lacking in common interests, and the cases were but few where they disagreed on the principles for the education of the children.

On the whole I think that it is safe to say that the mother was the chief and central character in most married lives in my material. In no less than 18 out of the 49 marriages did she contribute to supporting the finances of the home through an independent business or trade.

Illustrating the primary attitude of parents, more particularly mothers, to patient: in 27 cases they told me, more or less spontaneously, that at first they had not wanted the child. Among these, however, were six children born out of wedlock. And in most of the other cases the mother said—and I found no objective reason for doubting—that she had fully accepted the child when it was born or immediately afterwards. Only in four cases did the mothers explicitly give vent to an ambivalent attitude to the patient, secondarily she tried to compensate for this attitude by strong overprotection.

Finally it should be stated that in 16 cases the parents had married when or solely because the mother was pregnant, in 7 cases she expected the patient.

BRUCH stresses the insufficient suckling and often abnormally prolonged feeding by bottle of obese children. On this subject I can give information about 57 cases. Of these 16 children had not been suckled at all or for less than six weeks, whereas 15 patients had been suckled for more than six months. There were but three cases of abnormally prolonged feeding by bottle.

And on the whole it was my impression that the Danish prophylactic welfare-work for children, through the health nurse institution, had been highly contributory to reducing the number of gross aberrations and nourishment problems during the first year. However, on the stage of transition from suckling to spoon-feeding the mothers seem to have tended to giving the children greater quantities of food than necessary. In some cases this motherly care has apparently brought about some surplus weight of the children already during the first year, but what the mothers could tell me or remember on this point was mostly coloured with great inaccuracy.

Considering the weights at birth for the whole material, these 61 represented an ordinary spread without tending to overweigh the number of children with great weights at birth. In 35 out of the 61 cases the patient's obesity was alleged to have existed 'always'. But thorough questioning reduced the number to twelve, who could be said with reasonable certainty to have been obese from the first year.

Of the remaining 23 'always' obese children, the bulk (viz. 18) have reached a clear accentuation of their obesity when they were between 6—10 years of age. Of the other 26 children 11 have got fat before they were six years old, 15 after that time. To sum up: 33 children, i.e. more than half the material, have become obese or have added noticeably to their former obesity after the sixth year. In 9 of these cases the parents themselves thought that there

was a connection between obesity and the beginning of school, as these children at that time appeared to have particularly great difficulties in adjusting themselves to other children.

In the whole material 11 obesity cases seem to have started or increased when the child was sent to hospital, in five of these cases the change took place after surgical operations. In all the cases the patients had, while bedridden or immediately afterwards, eaten considerably more than before, much cheered by their parents. In three cases the onset of obesity was unmistakably due to decease of father or at any rate to consequent social, economic, and psychological changes in the surroundings. Obesity in the family was a recurrent phenomenon. In no less than 47 out of the 61 families there were more than two obesity cases among the next of kin. A rough clinical judgement put down 28 mothers but only 8 fathers (out of the 61), as being moderately or clearly obese. Among the patients' 99 brothers and sisters, only 6 were obese, and 6 had been so formerly.

It was difficult to get exact knowledge as to the eating-habits in the homes. What the parents told me was hardly ever to be trusted, the statements being evasive if not positively misleading. Still, my objective observations, e.g. during visits paid to the homes, told me about great eating-habits in four fifths of the homes (viz. 48). The food seemed to be starchy, rich, and in itself obesity provoking. Vegetables were few and far between and limited to the summer months. In 54 cases (88.5 %) the mothers admitted that the patient was fond of food and eat a lot, but the confession was usually the result of elaborate discussion. Bodily activity was another subject about which it was hard to get definite information. But I think it would be fair to call it reduced, more or less so, in about two thirds of the cases. Among the obese children in BRUCH's material 40 % had been persistently enuretic. In my material 12 out of 61 patients showed this symptom. Of other symptoms often psychogenetically conditioned I can adduce that nine patients had recurrent fits of undefined probably psychogenic abdominal-aches, five complained of periodical, undefined headaches, three suffered from night terrors, three displayed extreme conduct disorders, two nail-biting, rhytmical head banging, and one suffered from excessive masturbation urge. Altogether 20 patients, i.e. less than one third of the material, displayed one or several symptoms indicative of more or less outspoken emotional disturbances.

Finally it should be mentioned that two children had a presumably cryptogenetic epilepsy; and one was word-blind.

As said, I have not made use of deep-probing psychology in my methods of investigation, and apart from what is reported above, I have not made up any inclusive characterization or estimation of the patients' emotional development. In the course of my ordinary conversations with these patients

they struck me as being much more difficult to contact emotionally than children generally. Intelligence tests (Binet-Simon) have only been made in four cases, but at a rough clinical estimate there was no intelligence defects in any of the children, and the whole material seems to show the usual dispersion within the normal ambit.

In my analyses of the emotional evolution of the parents and their social and psychological background I have, like BRUCH, hardly succeeded in obtaining full information about the fathers. BRUCH's characterization about them as weak, unaggressive, poorly equipped for holding their own socially only covers a minority, and most of them had no out-standing traits fit for generalisations.

But I have sufficient information about 54 mothers to illustrate the main features in their social and emotional evolution. Twenty-six (i. e. little less than one half of them all) displayed a series of common characteristics and points of apparent resemblance, which should permit a definition of a mother type that in many ways proves to be similar to those mothers of obese children, whom BRUCH describes.

A prevailing common denominator for these twenty-six mothers was their descent from profilic families. In many cases the mothers told me frankly that the conditions in the crowded homes of their childhood most definitely was the reason why they only wanted a few or no children when they were married. It was remarkable how often the childhood of these mothers bore the stamp of poor economic and living conditions, and at the same time they felt emotionally very much attached to the parents and the old home. Through their growing years these mothers seem to have developed a specific and fundamental attitude to such things as illness, health, eating-habits, and obesity. Thus most of them were abnormally concerned with and afraid of illness, and mostly in a way that was emotionally very immature and neurotic. Tuberculosis in particular (there were one or several cases of T. B. among the relatives in 13 of the 61 families) seems to be of decisive moment in this attitude, and T.B. was often the plea for the enormous importance they gave to ample food intake and surplus weight. Most of the 61 mothers were themselves fond of food and great eaters, and 28 of them were, as already said, obese, very often of a pronounced 'endomorphic' build. In their opinion good food was equivalent to copious and rich food; and copious eating was not only in itself a habit, a pleasure, or a consolation, but it was also beyond dispute a sign of health and a nearly infallible protection and means against diseases, chiefly tuberculosis. They were all very tolerant to obesity, and even extreme obesity was not to be looked upon as anything in itself pathological. On the contrary, they regarded eating inhibition, a poor appetite, a minor loss of weight as symptoms of failing health. It was also interesting to observe that whereas they considered a slender, leprosome build identical with 'leanness' and disposing to illness, they preferred to call their own obesity or that of the children 'powerful build'. Only a few mothers had been to the doctor solely on account of the child's overweight, and it had often attained spectacular dimensions before a mere accident brought the patient to doctor and hospital. A dominant part was played here by fear of 'metabolic diseases' in connection with the desire of hormonal treatment of the case. In 16 cases among the 25 boys the mothers said that they were worried about the boys' genital development. In a few other cases it was chiefly the patients probably seconda-

rily, psychological difficulties among other children, which had driven the parents to doctor and hospital. It was but rarely that the mothers at once accepted an abnormally increased food intake as the only explanation of the patients' obesity; and their interest and cooperation in attempting a dietary treatment was negligible. Accordingly the bulk of the patients had regained their former eating-habits and overweight soon after dismissal from hospital.

No less than 24 of the said 54 mothers displayed nervous, chiefly 'psycho-somatic', symptoms, to be examined for which more than half of them had been admitted to hospital. Only 12 fathers had psychical ailments.

In about one half of the 54 cases there seems to have been an abnormally increased emotional attachement of mother and obese child. The mother's attitude in these cases was purely and primarily overprotective; while, as formerly stated, only four cases gave definite support to a verdict of clearly ambivalent attitude, with secondary feeling of guilt and compensatory overprotection of the child.

It is my impression, often verified by the interviews, that the fundamental attitude of a great many mothers to the obesity problem as well as their points of view generally were rooted in certain medical, hygienic, and cultural influences common for their own time and for that of their parents. Thus, a great part seems to have been played by the fear, formerly immensely widespread, of many diseases, particularly tuberculosis. At the same time much can be traced to the arduous and often exaggerated propaganda for ample and vitamincontaining nourishment to the child to protect it against diseases and states of deficiency. Finally, the mothers had some superficial notions dating from the period when the results of endocrinological research and hormone therapy were prominent features in the daily press and the medical propaganda.

One otherwise normally intelligent mother put it this way, 'His aunt, my sisters, died of T.B., so I have always seen to it that he had something for a lean day. If he is only allowed to have water and a few vegetables, I think I'd rather he had a metabolic disease; he can get pills against that, can't he'.

It is my opinion that many of the characteristics which these mothers of adipose children display, can hardly be regarded as only typical or peculiar. I think it is much more probable that what we are up against is nothing more than abnormally pronounced and extreme instances of ideas and tendencies that at a certain period influenced the Danish average population. However, we must do without a corresponding examination of a normal population, which would be valuable for a closer estimation. Likewise, for illustrative reasons an analysis of lean, food-refusing children and their surroundings would be interesting.

To sum up, the methods of analysis which I have used (dispensing with investigatory methods of deep-probing psychology) have not enabled me to

recognize in a Danish material the typical exterior, social, and psychological structure which according to BRUCH characterize the surroundings of obese children. Most cases confirmed the abnormally increased food intake of obese children and their frequent bodily inactivity. The surroundings have chiefly presented many cases of family obesity, great eating-habits, and a tolerant attitude to these phenomena. The mothers have had certain points in common with their American fellow sisters, seeing that in about half the cases they have been abnormally apprehensive of illness, primarily overprotective towards the adipose child. However, this fundamental attitude seems to have represented an extreme exaggeration of a number of notions about such things as illness, health, eating-habits, and obesity; and these ideas will presumably be explainable as recurrent characteristics of the average population traceable to a number of ethnological, national, cultural, family, and psychological influences.

As said above, another method in analysing the material has aimed at *a direct diagnostic estimation of each separate obesity case*, out of the 61 in question. In that way I have attempted to estimate the importance which in my opinion could be attached to a psychogenic explanation that would make the obesity picture understandable. Under this aspect *the material has been divided up into three groups.*

The first group, nominated '*positive*', comprises nine cases and is made up of patients, in whom a psychogenic obesity is demonstrated with approximate certainty or probability. All the cases are about children who on account of irregularities in the surroundings have presented clear emotional disturbances combined with the symptoms: increased desire for food, and great food-intake, decreased activity and subsequent obesity. I have tried to demonstrate the connection between the patient's emotional development and his obesity in time, progress, and substance, a broad psychological interpretation of these items being the basis of the said connection.

Psychogenesis in the nine cases has apparently been of varying and mutually dissimilar nature. In only three cases have I found a convincing congruity with BRUCH's characteristic family frame and psychogenic mechanisms. To exemplify the latter I shall proceed to present a short summary of a case history.

Case History No 16 (179/46, A.K.H.)

Youngest of three girls, sent to hospital aged 5, with pronounced, universal obesity, 38.5 kg, 120 cm.

The mother came from a home where they were badly off, but where they used to eat much, and there was much obesity in the family. As a child she was also a capital eater and very fat, but she practised slimming arduously and sucessfully when, at the age of 18, she married the patient's father, who was 23 years her senior and suf-

fered from a serious and disabling heart-disease. The patient's home was very well-to-do, dominated by the overbearing, active mother, the father's illness, and discord in the parent's married life.

The patient was not wanted. She was not suckled, as the mother had to take complete charge of the father's big firm. When the patient was just over one year old, the father died, and the mother now left the patient wholly to the care of an elderly, obese, very imperious housekeeper, who has run the house for many years. Since her father's death the patient has used to eat enormously and incessantly, and she puts on fat by leaps and bounds. She was spoon-fed for an abnormal length of time, she orders food from the housekeeper, who is illness-fearing and overprotective and comforts the child with food. The patient is indolent beyond measure, she does not ever leave the house if not in a car, the houskeeper reads aloud to her, or they chat, and the girl must not play with the other children in the neighbourhood. The housekeeper assists her in dressing, accompanies her everywhere, calls for the doctor in season and out of season to have the child examined for infections, flat-foot, petty ailments, all the time blind to the real abnormality in the condition of the child. The patient holds absolute ascendancy over the home, her every whim is humoured. Even the mother, of whom the patient is rather critical, is afraid of her, avoids her as much as possible, and bribes her with sweets and cakes, or takes her out to luxurious dinners at expensive restaurants. The mother does not conceal her ambivalent attitude to the child, on the contrary she bluntly confesses her aversion or indifference to it, and declares point-blank that she tries to assuage her feeling of guilt by indulging the child and procuring great quantities of sweets and food for her.

In hospital the child proves to be extraordinarily intelligent (Binet-Simon: I.Q. 177), but emotionally immature to an amazing degree, with an outward 'adult', 'conversational' conduct, combined with infantile, hysteriforme reactions when her demands for food and attendance are disregarded.

On re-examination the patient, aged 8, weighs 47.5 kg and stands 145.6 cm. Her obesity is unchanged, so is the family frame; she does not go to school, but has a private tutor as she refuses to meet other children.

Epicrisis: the patient's outspoken eating-consolation, inactivity, and subsequent obesity I take to be part of her abnormal emotional development, apparently symbolic of her position and her defence against the surroundings. The mother's ambivalent and secondarily overprotective attitude is clear, and the case differs from BRUCH's in its structure only in so far as the surroundings are on a higher social and economic level, and then it is the housekeeper, and not the mother, who is the main food-giver.

Also the following case history has several points in common with BRUCH's typical constellation.

Case History No 4 (471/41 A.K.H.)

Girl, only child, sent to hospital eight-year-old with grievous, universal obesity: 48.3 kg/120 cm. Breastchild until aged five months she was sent to hospital for febrile convulsions, since then she has weighed too much, increasingly so after being in hospital for serious diarrheal disturbance.

The parents' married life was bad from the beginning. The mother was the daughter of a minor civil servant, who had seven children. There was a strong feeling of solidarity in the family, besides they had great eating-habits and were fond of the material side of life. The mother felt closely attached to her parents and her brothers and sisters. She has always been fat and a great eater. She lived at home until the age of 28 she met the patient's father whom she married on account of periculum in mora. The father is an only child from a home of low social and economic standard. He has always been selfish, callous, ruthless, brutal, only interested in making money by various, often shady, transactions as a wholesale dealer or a manufacturer.

Through her whole childhood the patients's home has been clouded by the outspoken difference between the parents and their constant, daily, economic, and matrimonial strife, which cannot be discontinued, partly because the father refuses his consent to a divorce, partly because the mother cannot make a livelihood for herself or even get rooms. The father is openly hostile to his wife and his daughter, he leads his own life at home, sleeps and has his meals in one of the familys' two small rooms, where he carouses and in periods has other women staying with him; while his wife and daughter lodge as best they can in the other room and the kitchen. The only contact between the parents is when they quarrel about the patient or about mony. The mother and the patient are both fat and great eaters, emotionally they are bound together in their union against the father. They live in complete isolation, meet nobody but the mother's family, who support them morally and sometimes with money. The patient has no friends of her own age because of the state of things at home. She is often dejected, is very sensitive, emotionally immature and weak, conforms to the mother's wishes in everything, eats immoderately, mostly for consolation. The mother has always spoilt her and ever since she was a baby overfed her. Her obesity grew profusely in connection with her stays in hospital, when the mother was obsessed with fear of losing her. The mother continues her solicitude, coddles her, is concerned about illness, neurotic, often dejected, occasionally she takes dessicated thyroid for her own obesity. During the years just before the patient was sent to hospital she had a slight diabetes mellitus for which she takes insulin, as she cannot stick to a diet sheet. The mother keeps a jealous eye on the movements of the patient, afraid of losing her emotionally, panic, stricken when the patient is ill; she ran for the doctor, terrified, when the patient's menses started already when she was about eleven.

On re-examination the patient is 12 years old, weighs 59.5 kg, stands 159 cm, appears to be only moderately obese. She now has a job in an office, she has lost weight, having slimmed for reasons of vanity. She still seems to be emotionally immature, labile, but of normal intellect; and apparently she has to some extent extricated herself from the dominant maternal influence. Not that domestic affairs have changed, but their psycho-traumatic effect on the patient seems to have declined.

Epicrisis: No proof of a fundamental ambivalent attitude in the mother. The patient's strong attachement to her mother, her eating consolation and obesity have been regarded as part of an emotional reaction on the conditions in the surroundings.

The following case history can be cited as an example of an obesity case whose psychogenesis is of a somewhat deviating nature.

Case History No 44 (1430/46 A.A.S.)

Boy, sent to hospital eleven-year-old for heavy obesity: 46.7 kg/144 cm. Always fat, a great eater, increasingly so during the years just before admission to hospital. The parents' married life was as bad as can possibly be imagined, they were divorced when the patient was six years old. The mother was slim, psycho-infantile, has never been interested in the patient, after the divorce she made a living chiefly as a prostitute among German soldiers during the occupation. The father's family was a good deal tainted psychiatrically. A brother of the father's was in a lunacy asylum, another was a drunkard and committed suicide by hanging. The father was slim, lean, as a young man he sailed as a cook on the seven seas, at the age of 24 he got acquired syphilis (Wassermann's reaction in blood and cerebro-spinal fluid always negative). From the age of 30 progressive bronchitis and asthma bronchiale, gradually invalid and bedridden for several months every spring, often in hospital. During his later years he was dejected, with a great consumption of spirits, concerned about his illness and the future chances of the patient. The patient has always been closely attached to his father and hostile to his mother. Since the divorce of the parents the father and the patient have lived alone. The father cooks the food and cleans the rooms, but they are squalid and his illness does not make things any easier; they live almost exclusively on public relief. The father is over-solicitous and over-protective, he is concerned about the patient and coddles him, lays great stress on making him eat much, gives him most of the mony for sweets and entertainment. The food is exceedingly monotonous, being almost exclusively bread and bacon, and then coffee and pastries. The patient is infantile, reacts with crying and screaming-turns if the father does not comply with his wishes on the spot. He is always hungry, eats all day, buys huge quantities of sweets, is indolent, inactive; he exploits the father outrageously, lies, pilfers, borrows mony of everybody, three or four times a week he goes to the pictures, takes a taxi to go there and another taxi to go home. He cannot get on with other children at all, they tease him; he plays truant from school and gets the father to cover him.

When the patient is 13 years old, the father committed suicide by sleeping-tablets without a clear immediate suicidal motive. For a time the boy is placed with a sister of the father's; he is dejected, cries all day over his father, eats immoderately and puts on weight enormously. He is then sent to an orphanage where at first he has great difficulties in adapting himself. Under a sensible pedagogical and psychological treatment he gradually falls in with the others, he begins to eat normally, he loses weight. On re-examination aged 14 he weighs 52.5 kg and stands 160 cm and can hardly be said to be clinically obese. He still appears to be emotionally immature and hampered, and it is difficult to get into touch with him. Development of intellect is normal.

Epicrisis: The miserable married life of the parents, their divorce, the father's illness and invalidity with subsequent social, economic, habitational, and psychological conditions, the eating-habits and the obesity provoking food, the father's overprotection and the patient's attachment to him have had a decisive and retarding influence on the patient's emotional and social development. His behaviour disturbances, eating-consolation, inactivity, and

obesity are taken as an expression of an emotional way of reacting on the specific circumstances that characterizes the surroundings.

The second group of patients, nominated as '*doubtful*', comprises 12 cases, in which I have found emotional disturbances in connection with psychotraumatic frame-constellations or conflicts, but where I have not with convincing certainty succeeded in proving any relation to the patient's greediness, possibly reduced activity, and obesity.

Case History No 61 (1954/48, A.A.S.)

Girl, aged 9 yars, eldest of three children, increasing obesity before admission to hospital. 40.5 kg/138 cm. The mother is slim, psychically of natural emotional and intellectual development. From a good home with great eating-habits, she was married at the age of 23 because she expected the patient. The father is spineless, unbalanced, during the war he went to Germany to work, came home in 1944, infected his wife with syphilis, after which they divorced. Then the mother got a job in a factory while her mother ran the house, cooked the food, and to some extent overfed the children.

The patient, who was four years old when the parents were divorced and who has really never known her father, was during the first years after the change in the surroundings somewhat psycho-labile, vulnerable, reticent, but then she developed normally corresponding to her age; in hospital she appears free, balanced, normally intelligent.

The mother is equable, without neurotic traits, has a good understanding of the patient's problems, thinks that the patient's obesity is due exclusively to habitual greediness prompted by the grandmother. Under instruction on this point the patient loses 4.5 kg weight in two months; is psychically unchanged.

Epicrisis: I should hesitate to regard the patient's obesity as psychogenically conditioned, as I have not found any certain relation between the parents' divorce, the patient's emotional reaction thereon, and the subsequent greediness and obesity, though a connexion cannot be wholly excluded.

The third and last group of patients, nominated '*negative*', comprises the bulk of my material, a total of 40 children, in whom I have found no reason for supposing obesity to be conditioned by specific psychogenic mechanisms or circumstances. Most obesity cases in this group can apparently be easily explained as a resonable outcome of great eating-habits in the family. The following example is a typical one.

Case History No 5 (491/41, A.K.H.)

Girl, sent to hospital five-year-old, always fat and fond of food, 43.8 kg 135 cm. Only child. Clear disposition for obesity on father's as well as on mother's side, both descended from innkeepers and restaurateurs. The mother was fat from a child, fond of food, somewhat illness-fearing, scared of a presumably family disposition for T.B. The father is a calm, even-tempered, pycnic, slightly obese type. Both of them are fond of food and great eaters. The patient is like them, only more so. She devours

enormous quantities of food in the private household and also surreptitiously in the kitchen of the parents' hotel. On re-examination the patient has for one year been away from home at a cookery shool, she has started slimming for reasons of vanity, she is 17 years old, weighs 68 kg, and stands 165 cm., clinically she can be regarded as no more than very slightly obese, her psychical development corresponds to her age, she is independent and intelligent.

Epicrisis: The family tolerance and tradition of obesity and great eating-habits are principally responsible for the development of the patient's obesity; whereas, despite ample information, her surroundings and emotional evolution rendered no clue to supposing that specific psychogenic mechanisms should be of decisive moment.

Taking the two groups, 'positive' and 'doubtful', together, it appears that these 21 patients have revealed disturbances in theire motional development which with more or less could be related to the development of their obesity. A second examination of the material brought out that these patients, as to the degree of their obesity, were to be found chiefly in the heavy end of the material. Thus, calculated according to the Nybølle-table already mentioned 17 of the 21 patients (81 %) were of more than 40 % overweight, and 8 (38 %) more than 70 % overweight. The corresponding figures for the whole material were, as said, 82 and 26 %. Though the size of the material hardly allows conclusions, these figures do nevertheless seem, to some extent, to support the hypothesis to which I have referred before, that psychogenetically conditioned obesity cases are found with striking frequency among the very obese children, at least it seems easier to prove it there. On the other hand, it is of course difficult to dismiss the opinion that the emotional disturbances in these children may in part be due to secondary psychological and social disadvantages on account of their extremely exceptional position.

Comment

A division and estimation of the material on the described diagnostic basis must be of limited value. Much will depend, not only on the composition of the material and the methods of investigation, but also on the investigator concerned, on his individual powers to obtain the apparently relevant information, his ability to identify himself with his object, and—last but not least—his particular psychological orientation. If the latter has psychoanalytical bearings, then it will probably be easier to accept a psychodynamic explanation. It often seems easier to demonstrate apparently relevant psychogenic components in a family frame than generally supposed, whereas it is more difficult to decide the importance that can be attached to them, if

at the same time we want to bear in mind the predisposed somatic and psychical potentialities of reaction in each individual patient.

BRUCH points out that she does not look upon the family constellation described by her as specific in the sense that it is obesity-provoking in itself; but it must be regarded as a decisive factor which combined with a certain 'constitution' will result in the development of obesity. However, it seems as if BRUCH in her latest publications gives to the family frame a less decisive prominance, while shifting the preponderance to psychiatric-psychological studies of the primary, emotional structure of the personality of obese children. But her account, so far, of these investigations is little detailed and without documentation. Whereas BRUCH's observations originally built on a descriptive analysis of the family frame of obese children, the formulation of her theory is set forth chiefly on a foundation of ideas from psychoanalysis and deep-probing psychology. However, valuable continued studies under this aspect may be as contributory to a more profound understanding of the importance of emotional reactions in obese children it will still be more interesting (along the lines laid out by BRUCH) to inquire into the family frames of other groups of children, particularly into nonselected, normal material. If the information procured in this way should conform with the examinations of fat children in so far as they tend to weaken the importance that can be attached to certain family constellations and conflict situations for the development of psychosomatic conditions, then it would be reasonable to strengthen the intensity of research as to the individual predisposed personality structure and its significance for the choice of the way in which a patient reacts psychically and somatically.

Summary

In the light of BRUCH's works and theory, psychogenic aspects of childhood obesity have been estimated on the basis of a re-examination of 61 obese children. An account is given of the material and the methods of investigation.

It has not been possible to prove a characteristic outward social, family, and psychological constellation of surroundings for obese children. Recurrent characteristics in the surroundings are frequent occurrences of obesity in the families, great eating-habits, and a wide-spread tolerance of these phenomena. Most cases have confirmed that obese children have an abnormally great food intake, often combined with bodily inactivity. In their attitude to the fat child and in their views on such subjects as health, illness, eating-habits, and obesity, a great percentage of the mothers have displayed many points of resemblance and common characteristics, which are interpreted as extreme and abnormally exaggerated expressions of traits that presumably were universal and typical of the Danish population of a certain period. Nothing has been found that can justify the assumption of a recurrent ambivalent attitude with secondary overprotection on the side of the mothers.

By a direct diagnostic estimation of each separate obesity case in the material 9 cases were nominated 'positive'. 12 'doubtful', 40 'negative' with regard to psychogenic obesity. The criteria for this division are discussed, and a few typical case histories are presented in condensed versions.

Finally, attention is called to the desirability of procuring comparable control materials.

Au sujet de l'obésité psychogénique chez les enfants. II.

A la lumiére des travaux et de la théorie de BRUCH, les aspects psychogéniques de l'obésité de l'enfance ont été étudiés au moyen d'un nouvel examen de 61 enfants obéses. On donne un exposé du material et des méthodes d'investigation. Il n'a pas été possible de prouver l'assemblage caractéristique social, extérieur familial et psychologique de l'entourage des enfants obéses. Les caratéristiques que l'on retrouvent principalement sont dans l'entourage, le nombre fréquent des obésités dans la famille, le grand appétit habituel, et une tolérance largement étendue de ce phénomène, La plus part des cas ont confirmé que les enfants obéses avaient un besoin anormal de nourriture associé souvent à une certaine inactivité du corps. A propos de leur attitude vis-à-vis des enfants gras, et a propos de leurs vue sur des sujets comme la santé, la maladie, les habitudes de manger et l'obésité, un grand pourcentage de mères ont exposé des points de vue semblables et des caratéristiques communes, qui ont été interprété comme les expressions extrèmes et anormalement exagérées de points de vue qui étaient certainement habituels et typiques de la population danoise, a une certaine période. Rien n'a pu être trouvé qui puisse justifier la supposition d'une attitude ambivalente récurrente avec une hyperprotection secondaire du coté des mères. Au moyen d'une estimation diagnostique directe de chaque cas isolé d'obésité parmi le matériel, 9 cas furent trouvés positifs, 12 douteux et 40 négatifs en regard de l'obésité psychogène. Les critères de cette division sont discutés.

Psychogene Fettsucht bei Kindern. II.

Im Lichte BRUCH's Werk und Theorie wurden die psychischen Aspekte bei der kindlichen Fettsucht auf Grund einer Überprüfung von 61 fettsüchtigen Kindern vorgenommen. Über Untersuchungsmethoden und Material wird Bericht erstattet. Es war nicht möglich, ein charakteristisches Milieu, charakteristische Familien- oder Umgebungsverhältnisse für fettsüchtige Kinder zu finden. Wiederkehrende Erscheinungen in der Umgebung sind die Häufigkeit von Fettsucht in der Familie, die Gewohnheit grosse Mengen zu essen, und eine weit verbreitete Toleranz dieses Phänomens. Die meisten Fälle ergaben eine abnorm grosse Nahrungsaufnahme der fetten Kinder, oft gepaart mit körperlicher Inaktivität. In ihrer Haltung zum fetten Kind und in der Ansicht über Begriffe wie Gesundheit, Krankheit, Essgewohnheiten und Fettsucht hat ein grosser Prozentsatz der Mütter viele Punkte von Ähnlichkeit und gewöhnlicher Charakteristika entfaltet, welche als extreme und abnorm übertriebene Ausdrucksformen von Ansichten interpretiert werden, die allgemein und typisch für die dänische Bevölkerung eines gewissen Zeitabschnittes waren. Nichts konnte gefunden werden, was die Annahme einer sekundären Überprotektion von Seiten der Mütter rechtfertigen könnte. Bei einer direkten diagnostischen Wertung jedes einzelnen Falles von Fettsucht wurden im Material 9 Fälle als „positiv", 12 als „zweifelhaft", 40 als „negativ" im Bezug auf psychogene Fettsucht bezeichnet. Die Kriterien für diese Unterteilung werden diskutiert und einige typische Krankengeschichten werden gekürzt wiedergegeben. Schliesslich wird die Aufmerksamkeit auf die Dringlichkeit von verwertbarem Vergleichs-Kontrollmaterial gelenkt.

Sobre la obesidad psicogénica en los ninos. II.

A la luz de los trabajos y de la teoría de BRUCH se ha reexaminado a 61 niños obesos sobre los aspectos psicogénicos que dicha obesidad pudiera presentar. Se aporta un resúmen del material y de los métodos de investigación. No ha sido posible probar una característica falta de cuidado social familiar y psicológica del medio ambiente del niño obeso. Características recurrentes en los alrededores son frecuentes en las familias de obesos con ábitos muy comedores y una amplia tolerancia de este fenómeno. En la mayor parte de los casos se ha confirmado que los niños obesos reciben una cantidad elevada de alimento frecuentemente combinada con una inactividad corporal. En la actitud frente al niño obeso y en sus puntos de vista frente a cuestiones como salud, enfermedad ábitos de alimentación y obesidad un elevado porcentaje de las madres han demostrado algunos puntos parecidos y características comunes, lo cual es interpretado como expresiones exageradamente estremas y anormales de rasgos que presumiblemente eran universales y típicos de la población danesa en un cierto período. No ha sido encontrado nada que pueda justificar la presunción de una actitud recurrente ambivalente con una sobreprotección secundaria por parte de las madres. Haciendo una estimación diagnóstica directa de cada caso de obesidad por separado de este material 9 casos pueden catalogarse "positivos", 12 "dudosos" y 40 "negativos" en lo que hace referencia a obesidad psicogénica. El criterio para esta división es discutido y un corto número de historia clínicas típicas se presentan de un modo resumido. Finalmente se llama la atención sobre la necesidad de procurarse series de material de control comparable.

Received 25.4. 1952.

Aarhus Kommunehospital
Aarhus, Denmark.

Acta Pædiatrica **42**: 147—156. March 1953

From the Pediatric clinic of Karolinska Sjukhuset, Stockholm, Head: Prof. A. WALLGREN, and the Department of Ophthalmology, Sabbatsbergs Sjukhus, Stockholm, Head: I. KUGELBERG M.D.

The Supply of Oxygen to Prematures and the Appearance of Retrolental Fibroplasia

by A. HUGGERT

In a previous report the author gave an account of the picture of the fundus in premature children with special regard to retrolental fibroplasia. In a large number of the cases in this material there was manifest a peripheral oedema in the fundi as well as changes in the calibre of the vessels whilst in rather more than a quarter of the cases there was a picture that was similar to that which is described as being the earliest stage of retrolental fibroplasia. It was supposed that these changes were due to the degree of the infant's development at birth, but at the same time it was pointed out that the findings could also be explained as being due to a change in the oxygen tension of inhaled air in accordance with SZEWCZYK's hypothesis.

The material that was previously published (January, 1952), comprised 66 cases of premature infants with a birth weight below 2,600 grams. It has now increased to 130 cases, all of whom have been examined in the manner previously described. The findings in the fundi of the latter half of the material were similar to those reported previously. Out of 130 cases, 33 have shown more pronounced changes in the fundus of the type described as type 2 and 3 in the previous material. Of these 33 cases, 2 belonging to the latter half of the material gradually showed a fully developed retrolental fibroplasia. A report on the fundus pictures during different occasions when these two children were examined shows the following:

Case No. 89. Birth weight 1,360 grams. First examined four days after birth when some remnants of a. hyaloidea were found, but no remnants of the tunica vasculosa lentis. The retinal vessels, especially the arteries, were extremely narrow. The periphery of the fundus appeared to be normal. During the succeeding month the condition was more or less unchanged, the vessels were narrow and there were white papillae, but then, when the child was 2 months old, one found grey papillae, wide vessels all over the fundus, wide, previously invisible vascular connections peripherally and oedema in the periphery (type 2). One week later the oedematous changes had almost disappeared, but there was no change in the width of the vessels during the whole of the following month. A local connective tissue membrane was noticed in one place

pheripherally. The child never came back for further examination. When the child was 5 months old, the mother noticed that it seemed to see badly, and took it for examination when a bilateral retrolental fibroplasia was diagnosed.

Case No. 91. Birth weight 1,580 grams. Examined for the first time when it was five days old, when some remnants of a. hyaloidea together with remnants of pupillary membrane-vessels lying peripherally in the pupil were observed. The vessels of the fundus were narrow. Peripherally, the picture was not clear. One week later both papillae were white and the retinal vessels were as narrow as a thread. This picture remained unchanged until about one month after birth when one observed grey papillae, dilatation of the vessels that was more pronounced in the veins, newly formed vessels peripherally and oedema (type 2). For a further six weeks this picture remained more or less the same but one saw, however, in some places in the neighbourhood of the ora serrata, some greyish ridges with branching vessels on the surface, and when the child was discharged from the children's hospital it was considered as being a suspect case of retrolental fibroplasia. The child was never brought back for a control examination, and was not seen again until, at the age of five months it was taken to another ophthalmologist who diagnosed it as a case of developed bilateral retrolental fibroplasia.

Both of these cases, then, had a relatively low birth weight which, according to the general opinion, predisposes to retrolental fibroplasia. In addition they both manifested pale fundi during a very early stage with white papillae and extremely narrow retinal vessels. This decrease in the calibre of the vessels was most noticeable in the arteries. Relatively suddenly, the vessels then appeared to be markedly dilated, and peripherally one saw small vessels that had not been visible before as well as oedema. The dilatation of the vessels was, as also pointed out by many authors, most pronounced in the veins. If one makes a closer inspection of the records one finds that, from the time of their birth, both cases were treated in incubators with extra supplies of oxygen. The oxygen (45 % O_2) was administered for 24 hours a day for about one month when it was reduced to 2 hours for one day and then dispensed with altogether which is a rather sudden change. During the whole of the time that oxygen was being administered one observed these narrow vessels and white papillae, and in both cases the abnormal increase in the width of the vessels was noticed at the first examination that was made after the administration of oxygen had been discontinued and which, in both cases, was 3 days after the 24-hour administration had been stopped.

This connection between the breaking off of the oxygen administration and the change in the picture of the fundus has also been observed in other cases in our series that did not develop into retrolental fibroplasia (see below). As oxygen administration has been reported in the works of CAMPBELL, CROSSE, SCEWCZYK and others as a possible cause of retrolental fibroplasia this connection gave rise to a closer investigation of the administration of oxygen in the whole of the controlled material.

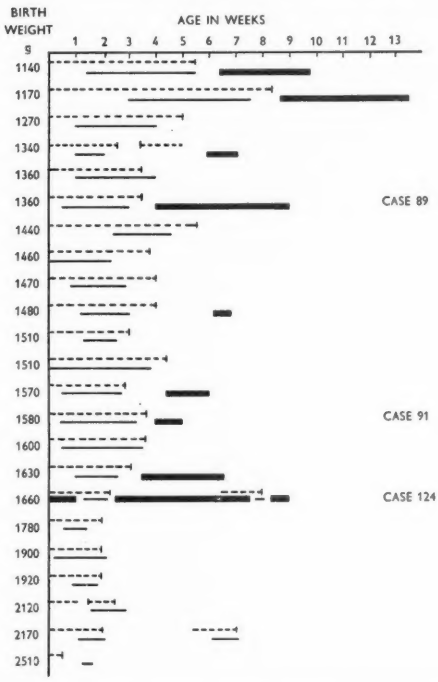

Table 1. The occurrence of extremely narrow retinal vessels (———) and palpably wide ones (▬▬) in relation to the time of administering oxygen (- - - - - - -). For those times when the calibre of the vessel is not given, there has either been no examination, or else the vascular caliber was not changed noticeably or only slightly.

In the whole material, one found 27 cases that had had extremely narrow vessels during one or other of the occasions when examined. All of these were treated in an incubator with an extra supply of oxygen. As already pointed out in the previous work, the majority of them manifested a sudden transition to wide retinal vessels and peripheral oedematous changes. In Table 1, 23 of the cases with narrow vessels are included, and the appearance of the vessels is placed in relation to the time of the administration of oxygen. Of the other 4 cases, no information could be obtained in regard to the administration of oxygen in respect of one case whilst the remaining 3 cases all died after a relatively short time during the administration of oxygen, for which reason they have not been included. The 27 cases do not comprise all cases that had received extra oxygen, but in the others, however, the width of the vessels has not been registered carefully enough during the different occasions of examination.

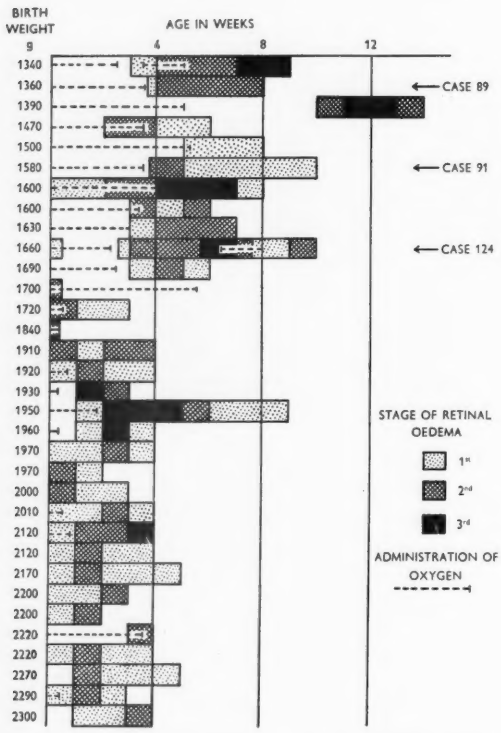

Table 2. The occurrence of the different stages of retinal oedema placed in relation to the administration of oxygen in the 33 cases with more pronounced retinal changes.

It appears rather clearly from the table that a transition from extremely narrow vessels and white papillae to wide vessels and grey papillae takes place within a few days after leaving off the administration of oxygen. As it was only possible to show extremely narrow vessels in cases that had been given an extra supply of oxygen, the connection between the administration of oxygen and the narrow retinal vessels ought to be unmistakable. It would seem that the connection in these cases between the cessation of oxygen administration and the increase in the width of the vessels, especially the veins, is equally unmistakable. The very rapid disappearance of a. hyaloidea and the pupillary membrane vessels, which disappear intra-uterine at a later stage, also indicate an influence of the oxygen on the width of the vessels.

Extremely narrow retinal vessels of this nature have not been observed in all the cases that manifested peripheral changes in the fundus similar to those

that arise in the earlier stages of retrolental fibroplasia, for which reason, and in order to get another aspect of the problem, all 33 cases have been included in Table 2 that have manifested a more pronounced degree of oedema, that is to say, types 2 and 3 of the fundus changes, and the appearance of the fundus is placed in relation to the time when oxygen was administered.

Of these 33 cases, then, 13 were given extra oxygen for 14 days or more, 11 were not given any extra oxygen at all, and 9 cases were given extra oxygen for only a few days. One can see from the table that, generally speaking, dilatation of the vessels and oedema was registered fairly soon after birth in those cases that had not been given extra oxygen, and, in the case of the others, especially when the administration of oxygen had been left off. Nevertheless, it will be seen from the table that in some cases pronounced oedema was registered during the time when extra oxygen was being given (see, for instance, the case with the birth weight of 1,470 g and the two that weighed 1,600 g at birth), for which reason the connection between the cessation of oxygen administration and the manifestation of oedema is not so unmistakable as the connection between the width of the vessels and the administration of oxygen. It might perhaps be well to mention here that examinations of the fundi were only carried out once a week, and for this reason it has not been possible to give the exact time when the change in the fundus picture took place and which might have happened during anything up to one week prior to its having been registered. Therefore, in many of the cases there was probably a change in the fundus picture, compared with the preceding examination of the eyes, that could have been established several days before the examination was made. As even children, that have not had any extra oxygen, have manifested dilated vessels and oedema, one is bound to suppose, in these cases, that the vascular dilatation has had some connection with the transition from the intra-uterine to the extra-uterine life and has had something to do with the incomplete development of the retina in prematures.

In the author's previous work one found a connection between the birth weight and the time when there was a manifestation of oedema and vascular dilatation in the retina so that the lower the birth weight was, the later one found the changes. However, it was then pointed out that the prematures that had had a lower birth weight were treated in a different way to those with a higher birth weight. From the connection found between the manifestation of fundus changes and the administration of oxygen, it may therefore be considered probable that it is the extra administration of oxygen that has some special connection with the fundus changes of the type of retrolental fibroplasia in the early stage, even though one should not overlook the different degrees of development of the retina at birth in the different cases.

CAMPBELL, CROSSE and others have previously presumed that a direct toxic effect of oxygen was the cause of retrolental fibroplasia, whilst SZEWCZYK assumed that this develops because of a relative anoxia in the tissues when the child is suddenly transferred from an excess of oxygen to a normal oxygen content. Both of these opinions could be equally probable as causes of the observations made here.

In the earlier work a more cautious attitude was taken in regard to the connection between the fundus findings that were made and the earlier stages of the retrolental fibroplasia. As now 2 of the cases which have had these fundus changes, and which otherwise were not of the more pronounced kind, later developed into retrolental fibroplasia, the connection should be more obvious. Therefore these vascular changes and peripheral oedema of types 2 and 3 must be regarded most probably as being early stages of retrolental fibroplasia, and even the type 1 that was described as showing very mild changes must, in principle, be regarded as being the same picture of the disease. As previously mentioned in brief, the enlarged material showed, as did the earlier material, these early changes with a yellow-white reflex peripherally and a suspected oedema in the periphery of the retina in approximately $^2/_3$rds of the cases, and in about $^1/_4$th of all cases a more pronounced oedema with retinal changes of types 2 and 3. It should also be mentioned that there were some cases that, simultaneously with the vascular dilatation in the retina, manifested dilatation of the vessels of the iris that was visible to the naked eye with simultaneous changes in the colour of the iris.

All in all, then, 9 cases manifested this vascular dilatation in the iris which, in 3 of them, was so pronounced that the colour of the iris changed from grey-green or blue-green to red-brown in order then to revert to its original colour in about a week. As this vascular dilatation in the iris which makes its appearance during the early stage, is more often a very rapid transition, it is quite probable that, similar to the rapidly transient retinal changes of type 1, it occurs considerably more often than can be discovered during ocular examinations that are made only once a week.

The connection that has been established here between the changes in the oxygen content of inhaled air and the manifestation of the early stages of retrolental fibroplasia, gives additional support to the opinion primarily expressed by CAMPBELL, CROSSE and SZEWCZYK, namely that changes in the oxygen content bring about retrolental fibroplasia. But it is not possible to decide with any degree of certainty whether the developing factor is the toxic effect of oxygen according to CAMPBELL and CROSSE or whether SZEWCZYK's theory about the relative anoxia that sets in after the administration of oxygen has been left off is the cause. That similar changes have been observed in

children who have not been given oxygen (see Table 2) and then are present immediately after birth, backs up SZEWCZYK's opinion to some extent. On the other hand the occurrence of retinal oedema during the time when oxygen is being administered is more indicative of a toxic effect of oxygen. Some other published investigations point to the same direction, and it should be especially emphasized that PATZ, HOECK and DE LA CRUZ have seen a retrolental fibroplasia develop in many cases during continuous administration of 65—70 % oxygen. As the author has pointed out in his earlier work, it is probable, that one must reckon partly with the degree of development in the child as being the cause of the milder retinal changes in the periphery, and partly with a further factor as being the cause of retrolental fibroplasia: everything appears to indicate that this latter factor can be the oxygen therapy. As the frequency of the disease in most countries with the exception of the United States is so low a clinical observation of the part played by the oxygen administration can only be achieved if American clinics with a hitherto high frequency of retrolental fibroplasia would, if possible, leave off the oxygen treatment of prematures for some time. A decisive proof, however, can probably only be obtained from making experiments on animals (GYLLENSTEN & HELLSTRÖM).

In this connection some further viewpoints can be submitted in regard to the problem of retrolental fibroplasia. It would seem that retrolental fibroplasia has never, or at least very seldom, occurred before 1941 after which it was first established in USA and then its frequency rose rapidly. The first known cases in Sweden were born in 1944 and 1945. Incubators with special oxygen administration began to be generally used in USA in about 1940 and in Sweden 1944. In Sweden the incubators used are those that give a content of 45 % O_2 whereas many of the models used in USA give between 60 and 80 % oxygen content (see SZEWCZYK). If the oxygen content as such or the rapid change over from a high oxygen content to a normal one is the developing factor in retrolental fibroplasia, the strain will nevertheless be greatest in both cases in the higher oxygen tension of the American models, which might be an explanation for the much higher frequency of retrolental fibroplasia in certain quarters and especially in USA. For that matter it appears from the ever increasing literature on the subject in 1952, that when using incubators with 50—80 % oxygen one obtains more pronounced retinal changes with, amongst other things, profuse hemorrhages in the corpus vitreum than could be registered in the present material (see, for instance, BOUSQUET and LAUPUS). Information has even been received from Australia about the occurrence of retrolental fibroplasia first when effective incubators with a high oxygen content began to be used (1948), whereas, previously the disease was unknown (RYAN). GOLDMANN and TOBLER give an account of similar experiences from

Switzerland. Similarly, the occurrence of the disease in France might almost be placed in connection with the time when extra oxygen was administered (LELONG *et al.*).

CROSSE and EVANS of Birmingham have ceased to administer oxygen other than in dangerous cases of asphyxia, with the result that no cases of retrolental fibroplasia have occurred since this change was brought about. RYAN gives an account of similar experiences from Australia and points out that the slight changes, corresponding to the author's type 1, have not decreased in frequency, which indicate that these changes have not the same cause as definitely formed retrolental fibroplasia.

As SZEWCZYK pointed out one may also reckon with vascular changes occurring not only in the retina, but also in other parts of the body, and not only in prematures but even in other newly born infants that are given extra supplies of oxygen. Observations of vascular dilatations in the iris support this opinion in the same way that previous observations of hyperemia and hemorrhages in the internal organs and central nervous system in prematures do. This should even be the explanation of the fact that KRAUSE, in a large number of cases of retrolental fibroplasia found, simultaneously, cerebral symptoms (encephalo-ophthalmic dysplasia). However, it must also be mentioned that there are several investigators who think that there is no evidence that oxygen is an etiologic factor in retrolental fibroplasia (see ZACHARIAS and BEMBRIDGE *et al.*).

Finally, it may be said that one of our latest controlled cases (No. 124), manifested such pronounced retinal changes of the early retrolental fibroplasia type, that it had to be replaced in an incubator after some time and be treated with oxygen. In connection with the oxygen treatment (approximately 60 % O_2) there was a reversion of the retinal changes such as previously reported by SZEWCZYK. As, later on, the oxygen was gradually reduced, there was a reappearance of the vascular dilatations in one of the eyes which lasted for about a week and then disappeard. As this case has not been finally checked and the final course in respect of the eventual appearance of a fully developed retrolental fibroplasia cannot yet be determined, a more detailed report of the case together with the result of the treatment must be deferred until a sufficiently long time has elapsed after treatment.

Summary

The importance of oxygen administration in regard to the manifestation of changes in the calibre of the retinal vessels as well as the presence of peripheral retinal oedema has been studied from a material of 130 premature infants. It appears that the retinal vessels were often very narrow during the administration of oxygen, and that vascular dilatation and peripheral oedema occurred in most cases when oxygen was stopped,

but, in individual cases, even whilst oxygen was being administrated. In the cases that had not been given oxygen, dilatation of the vessels and oedema occurred immediately after birth. Of those that were treated with oxygen, 2 developed into retrolental fibroplasia. Finally, attention is drawn to the connection between the time when retrolental fibroplasia made its appearance in different countries as well as the time when incubators with surplus oxygen began to be used in the respective countries.

L'apport d'oxygène aux prématurés en rapport avec l'apparition de fibroplasie rétrolentale.

L'importance de l'administration d'oxygène en rapport avec des modifications du calibre des vaisseaux rétiniens et également la présence d'un oedème périrétinien a été étudiée sur 130 prématurés. Il ressort de cette étude que les vaisseaux rétiniens étaient souvent très fins pendant l'administration d'oxygène et qu'une vasodilatation et un oedème périphérique était observés dans la plupart des cas dès que l'on cessait les administrations d'oxygène, mais également dans quelques cas individuels aussi pendant l'oxygénothérapie. Dans les cas qui ne recurent pas d'oxygène, la vasodilatation et l'oedème apparurent aussitôt après la naissance. Parmi ceux qui furent soumis à l'oxygénothérapie, deux développèrent cependant une fibroplasie rétrolentale. En conclusion, l'auteur attire l'attention sur le moment où la fibroplasie apparait dans différents pays en rapport avec la date à laquelle on mit en service des incubateurs donnant un surplus d'oxygène dans ces pays respectifs.

Die Sauerstoffversorgung der Frühgeborenen und das Auftreten der retrolentalen Fibroplasie.

Die Bedeutung der Sauerstoffzufuhr in Bezug auf das Auftreten von Kaliberveränderungen der Retinagefässe als auch auf das Vorliegen von peripheren Retinaödemen wurde an einem Material von 130 Frühgeborenen studiert. Es scheint, dass die Retinagefässe während der Sauerstoffzufuhr oft sehr eng sind, und dass Vasodilatation und periphere Ödeme in den meisten Fällen auftreten, wenn die Sauerstoffzufuhr gestoppt wird, in Einzelfällen aber während der Sauerstoffgabe. In Fällen, in denen kein Sauerstoff gegeben wurde, traten Blutgefässerweiterung und Ödeme gleich nach der Geburt auf. Von den mit Sauerstoff behandelten Frühgeborenen entwickelten 2 eine retrolentale Fibroplasie. Schliesslich wird die Aufmerksamkeit auf die Zusammenhänge zwischen dem Zeitpunkt des Auftretens der retrolentalen Fibroplasie in verschiedenen Ländern, und der Einführung von Inkubatoren mit Sauerstoffübersättigung in den betreffenden Ländern, gelenkt.

La administración de oxígeno a prematuros y la aparición de fibroplasia retrolental.

Se ha estudiado la importancia de la administración de oxígeno con respecto a la manifestación de cambios en el calibre de los vasos de la retina así como la presencia de edema retinal periférico en un material de 130 niños prematuros. Parece ser que durante la administración de oxígeno los vasos retinales son amenudo muy delgados y que la dilatación vascular y el edema periférico se producen en la mayoría de los casos cuanda se suspende la administración de oxígeno, pero en algunos también durante la misma. En los casos en los que no se dió oxígeno, la dilatación de los vasos y el edema ocurrieron inmediatamente después del nacimiento. De los casos que se trataron con oxígeno se desarrolló una fibrosis retrolental en dos. Finalmente se llama la atención

sobre la relación entre el tiempo en el que la fibroplasia retrolental hace su aparición en diferentes países y el tiempo en que las incubadoras con un surplus de oxígeno empezaron a usarse en los respectivos países.

References

Bembridge, A. A., Coxon, M., Houlton, A. C. L., Jackson, C. R. S. and Smallpiece, V.: Retrolental fibroplasia. A problem of prematurity. Brit. M. J. p. 675, 1952.

Bousquet, F. P. and Laupus, W. E.: Studies on the pathogenesis of retrolental fibroplasia. Am. J. Ophth., *35:* 64, 1952.

Campbell, Kate: Intensive oxygen therapy as a possible cause of retrolental fibroplasia: a clinical approach. M. J. Australia, *38:* 48, 1951.

Cross, Mary V. and Evans, P. J.: Prevention of retrolental fibroplasia Arch. Ophth., *48:* 83, 1952.

Evans, P. J.: Retrolental fibroplasia. Tr. Ophth. Soc. U. Kingdom, *71:* 613, 1951.

Goldmann, H. and Tobler, W.: Zur Ätiologie der retrolentalen Fibroplasie. Schweiz. med. Wschr. *82:* 381, 1952.

Gyllensten, L. J. and Hellström, B.: Retrolental Fibroplasia-Animal Experiments. Acta Pædiat. *41:* 577, 1952.

Huggert, A.: The appearance of the fundus oculi in premature infants, with special reference to the early stages of retrolental fibroplasia. Acta Pædiat., *41:* 463, 1952.

Jefferson, E.: Retrolental Fibroplasia. Arch. Dis. Childhood. *27:* 329, 1952.

Laupus, W. E. and Bousquet, F. P.: Retrolental fibroplasia. Am. J. Dis. Child., *81:* 617, 1951.

Lelong, M., Renard, G., Rossier, A., Lemasson, C. et Michelin, J.: La rétinopathie des prématurés (fibroplasie rétrolentale). Presse méd., *59:* 705, 1951.

Patz, A., Hoeck, L. E. and De La Cruz, E.: Oxygen administration in retrolental fibroplasia. Am. J. Ophth., *35:* 1248, 1952.

Ryan, H.: Retrolental fibroplasia. Am. J. Ophth., *35:* 329, 1952.

Szewczyk, T.: Retrolental fibroplasia. Am. J. Ophth., *35:* 301, 1952.

Zacharias, Leona: Retrolental fibroplasia: A survey. Am. J. Ophth. *35:* 1426, 1952.

Received 28.10. 1952.

Ögonkliniken
Sabbatsbergs Sjukhus
Stockholm.

Acta Pædiatrica **42**: 157—165. March 1953

CASE REPORT

A Hyperacute Case of Erythroleukaemia Treated with Aminopterin

by KHO LIEN-KENG

From the Pediatric Clinic, University of Amsterdam
(Head: Prof. S. van Creveld M. D.)
and the Pathological Institute Binnengasthuis, Amsterdam
(Head: R. van Dam M. D.).

Introduction

On the strength of clinical, haematological and pathological findings in three patients with severe anaemia, fever, enlarged liver and spleen, pronounced erythroblastocytosis and marked proliferation in the erythroid system of the bone marrow and other organs, in which the course was invariably acute and the outcome fatal, Di GUGLIELMO (7) was of the opinion that this was a specific disease. He termed it "acute erythraemia," resembling a leukaemic process of the red system.

Since then numerous publications have appeared in the Italian literature referring to the "Malattia di Di Guglielmo."

MOESCHLIN (17) followed up all the cases published and came to the conclusion that, up to 1940, only five cases could be regarded as pure forms of erythraemia, namely: two cases of Di GUGLIELMO (7, 8) and one case of LAZARRO (11), BENEDETTI (1) and PARADISO (19). In the more recent literature one can find publications e.g. Di GUGLIELMO & QUATTRIN (9), LOCASCIO & POSTGLIONE (14), SARRAILHÉ (24) and FRADA (6), which fulfill the conditions of the pure form of the disease.

In the pure form one finds mainly nucleated cells of the red series and in the mixed forms also young myeloid cells. For this differentiation according to LEITNER (12) and STORTI (26) the vital marrow findings is of great importance. The pure form is characterised by predominance of the erythroid elements in the marrow. Most authors report a percentage of erythroblasts from 70 % to almost 100 % (1, 6, 7, 8, 11, 19, 24). In the mixed forms erythroblast percentages from 30 % to 70 % were found (2, 3, 5, 10, 15, 16, 18, 20, 21, 23). The presence of many myeloblasts in the blood in addition to the erythroblasts should favour a mixed form, according to HARVIER et al. (10).

As far as the nature of erythraemia and erythroleukaemia is concerned, most authors take it that this can be compared with a real leukaemic process. Many authors regard this disease as a neoplastic process (17, 23) and others as a hyperplastic process (7, 16). The aetiology remains obscure.

Case history

A previously healthy boy according to the parents, aged 7 months, was vaccinated against smallpox on 16.12. 1949. Pustules appeared after a few days and on the 9th

day after vaccination the upper arm was red and swollen and the patient was listless. Two days later the child became feverish, refused food and drink and vomited a great deal. The mother noticed that the patient was becoming increasingly pale. When the family doctor was called on 2.1.'50, he noticed that the abdomen was swollen, and as the condition did not improve the child was admitted to the Paediatric Clinic on the 9th January 1950. The patient was at the time the only child of healthy parents, neither of which were of Mediterranean origin. A younger brother who was born a year later had a normal blood picture. None of the family had previously suffered from any blood disease. A sister and a cousin of the father were said to have died of a tumour in the abdomen at the ages of 11 and 7 years respectively.

On examination the child looked ill, was pale, had a puffy appearance and was well nourished. He lay still in bed, did not play, but was not apathetic and reacted to the surroundings. The head, face and extremities were painful to the touch. Pulse: no abnormalities. Respirations: rapid (50/min); groaning with inspiratory retractions in the neck, intercostal regions and along Harrison's groove. The skin was very pale, not dehydrated. A haemorrhagic spot covered by a scab, was visible on the medial side of the left foot. On the back there was a swelling with a blue discolouration above the XIIth thoracic vertebra. There were no petechiae. On the right arm pox pustules were visible, three of which were covered with scabs. There was not much local reaction. The mucous membranes were very pale. The patient was not jaundiced, nor cyanotic. He had slight symptoms of rickets: bossing of the head, evident Harrison's groove, swollen wrists and curved tibiae. The lymphnodes were not enlarged. Heart: not enlarged. A soft systolic murmur could be heard over the heart. Lungs: W. C. Abdomen: swollen. *Liver:* 4 fingers below the costal margin in the median clavicular line. The consistency was firm, the edge rounded. The *spleen* reached down to the iliac crest and had a firm consistency. The testicles could be felt high in the scrotum. Reflexes: patellar and Achilles positive. Babinski positive on both sides. *Laboratory investigations:* blood cultures negative, Wa.R. and Kahn negative, icteric index 8, thymol turbidity test 6.7 units. Bloodgroup B Rh +. Urine: negative for albumin, sugar, acetone and bilirubin, positive for urobilin. Sediment: no abnormalities. Typhoid, paratyphoid cultures negative. Faeces: typhoid, paratyphoid and dysentery negative. X-ray investigations: left arm, right leg, spinal column no abnormalities, thorax no definite abnormalities. *Blood picture:* 8.1.'50: Hb 20 %, red blood cells 1.08 million, nucleated red cells 5,800, reticulocytes 25 ‰, thrombocytes 9,700, leucocytes 52,500 (young basoph. 1, young eo 2, myeloblasts 6, promyeloc 5, myelocytes 19, metam. 16, stabcells 7, polym. 15, monoc. 4, lymphoc. 24). Red cells fragility 0.48—0.40. There was anisocytosis, polychromasia, slight poikylocytosis, no target cells. Most of the nucleated red blood cells had a basophil (30 %) or polychromatophil (60 %) protoplasm and only a small number were oxyphil (10 %). Pro-erythroblasts were only found sporadically. Most erythroblasts were of the secondary type (normoblasts). The contours of the cells were often irregular. The nuclei were often polymorphonuclear in type with interlacings and lobules, falling apart in several segments. Nuclei containing very little protoplasm, mitotic divided cells and dissociation of maturation of nuclei and protoplasm were found. All cells of the myeloid series were represented. In general only a few atypical forms were found. Many of the myeloblasts were paramyeloblasts. In the young cells a dissociation between maturation of the nucleus and the protoplasm was often visible. Relatively many monocytes, and now and then also plasma cells were found. The lymphocytes showed no abnormalities. *Bone marrow* (see fig. 2): very rich in cells. It had a very strongly polymorphic character and con-

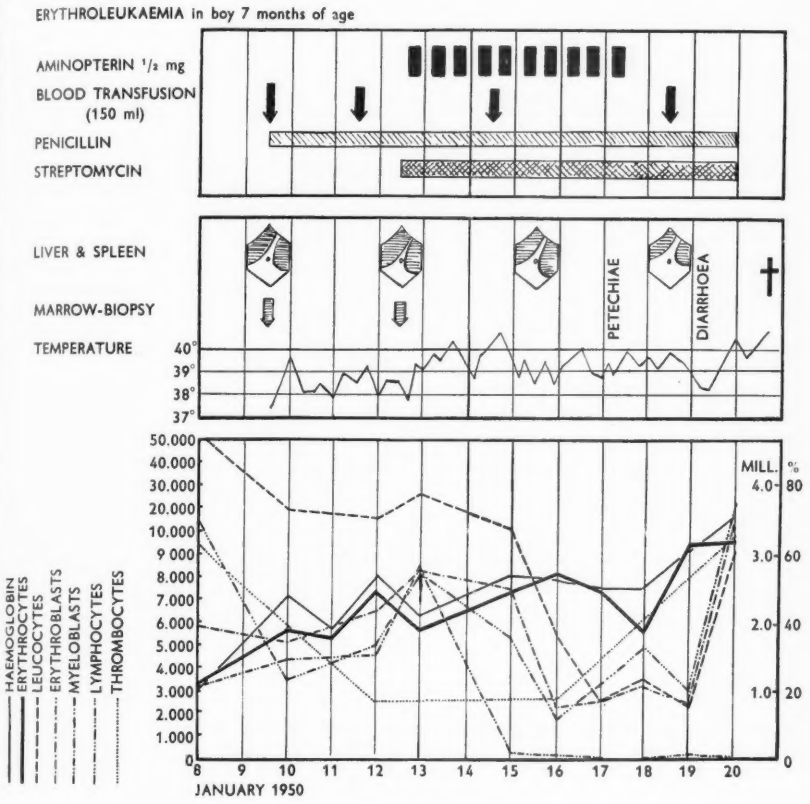

Fig. 1. Course of the disease.

tained no fat cells. In the marrow puncture of 9.1.'50 the ratio of myeloid and erythroid elements was 1 : 1, and three days afterwards 1 : 3.3. Differentiation: young basoph 0.4, young eo 4.2, mature eo 4.2, myeloblasts 20.0, prom. 11.4, myeloc 29.0, meta 10.6, stabcells 3.4, polym 5.4, monoc 0.2, lymphoc 12.0. On 100 leucocytes 16.0 pro-erythroblasts, 18.2 erythroblasts, 64.8 normoblasts, and 6.0 reticular cells. No megakaryocytes. All cells of the myeloid series were represented. Often atypical cells, also maturation dissociation between nucleus and protoplasm of the myeloid and erythroid elements were found. There was no increase of cells of the reticulo-histiocytic system. In the marrow of 21.1.'50 a marked increase of the erythroid cells was found (more than three times the white elements).

Treatment and course of the disease (fig. 1). In the beginning penicillin was administered, supported by blood transfusions. However when the condition did not improve and the diagnosis of a leukaemic process was certain, it was decided to administer aminopterin. The dosage was half a milligram twice daily. The patient was also given streptomycin. There was still no improvement in the general condition. The

temperature actually rose and varied between 38° and 40°C. On the 6th day petechiae occurred on the abdomen and the aminopterin was discontinued. Due to the influence of aminopterin the liver and spleen had become smaller. The influence of aminopterin on the different blood elements is shown in fig. I. Two days after the discontinuation of the aminopterin the patient developed diarrhoea and died suddenly the following day with hyperpyrexia.

Autopsy report: The skin showed some petechiae on the right upper abdomen and almost healed pox pustules on the right upper arm. The liver reached three cms. below the costal margin. No haemorrhages in the organs were found. The abdominal lymphnodes were slightly enlarged. Heart: enlarged, weight 50 g. Lungs: some collapsed areas. Liver: 530 g, smooth surface, firm consistency. Spleen: 200 g, smooth, firm consistency; on cross section red colour with dark patches (haemorrhages) and showing a recent infarct, follicles not clearly visible. Thymus, pancreas, adrenals, no abnormalities. Gastro-intestinal tract: scattered haemorrhages and swelling of the Peyer's patches. Kidneys, no abnormalities. Bone marrow: even dark red colour.

Microscopy: Liver: (fig. 4) the liver cells as well as the Kupffer cells were somewhat swollen. In the portal spaces as well as in the capillaries infiltrations of myeloid and erythroid cells were found. The erythroblasts often formed nests consisting of big cells with large nuclei with nucleoli. Spleen: the follicles had entirely disappeared except for a few concentrations of lymphocytes. The normal structure of the spleen was hardly recognisable. There was a tendency towards fibrosis of the trabeculae. The picture was characterised by marked infiltrations of polymorph cells and was dominated by erythropoietic nests. Nearly all cells of the myeloid series were represented, while there were also many eosinophil granulocytes. Lymphnodes: the pre-existent structure was still present, but everywhere myeloid and erythroid elements were found. Bone marrow: (fig. 3) very rich in cells and hardly any fat tissue. The normal marrow structure was no longer present and the formation and maturation zones could no longer be distinguished. The marrow was predominantly erythroblastic, although many young myeloid cells could also be found. Comparatively many eosinophils. No megakaryocytes were seen. There was no abnormal proliferation of the elements of the reticulo-histiocytic system. Kidneys: no abnormalities. Thymus: polymorphic picture with infiltration of myelocytes and erythroblasts. Ileum: there were many proliferations of myeloid and erythroid elements and reticulum cells in the submucosa.

Discussion

A previously apparently healthy boy of 7 months of age became ill shortly after vaccination against smallpox. He had fever, vomited and showed an increasing paleness. On admission to hospital he was found to have marked hepatosplenomegaly, severe anaemia, thrombocytopenia and leucocytosis. Many young myeloid cells and many erythroblasts were found in the peripheral blood. The marrow was characterised by domination of the erythroid over the myeloid elements. Many erythroblasts belonged to the group of para-erythroblasts as described by Rohr, while some atypical young leucocytes were also found (para-myeloblasts). The clinical and haematological symptoms and the quickly fatal outcome pointed to an erythroleukaemic disease. This diagnosis was later confirmed by the pathological and histological findings.

The development of the disease in our patient was very acute. Contrary to the findings of some French investigators (16) who reported progress of the process towards

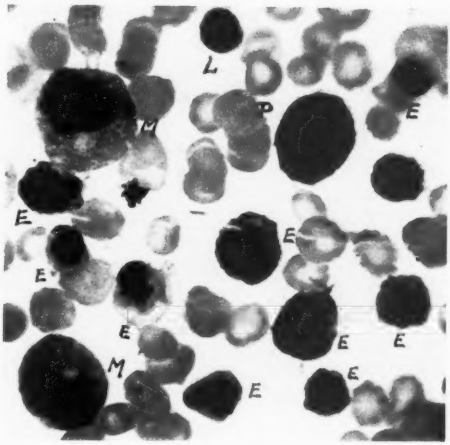

Fig. 2. Marrow film: Proerythroblast (P), erythroblasts (E), L = Lymphocyte and myelocytes (M). (1,000 ×).

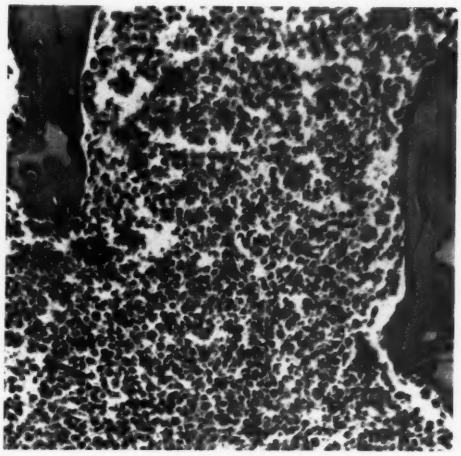

Fig. 3. Marrow section: highly cellular, loss of normal structure, no formation and maturation zones. (100 ×).

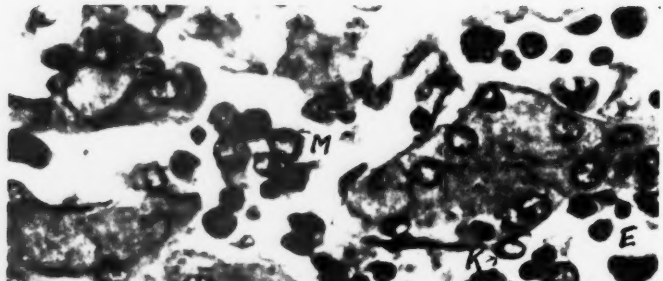

Fig. 4. Liver with erythroid (E) and myeloid (M) proliferations in the widened sinusoids, and swollen Kupffer cells (K). (500×).

a real leukaemic process, we observed in our case a tendency to change from an erythroleukaemic to a real erythraemic process. The aminopterin can only be partly responsible for this, since the tendency already existed previous to the commencement of this drug. The influence of the aminopterin on the different elements can easily be seen with the aid of fig. 1. The young myeloid elements (myeloblasts, promyelocytes, myelocytes) quickly disappeared from the peripheral blood, while in connection with this the liver and spleen became smaller. We had the impression that in this case the aminopterin acted in the first place upon the extramedullary sources. This corresponds with ROHR's hypothesis that the young myeloid elements in the blood originate from these sources in case of leukaemia. The influence of aminopterin on the other blood elements was not so pronounced. The number of erythroblasts and lymphocytes showed only a small decrease. We got the impression that the influence on the thrombocytes was of little importance, an observation which is in agreement with the findings in those cases where acute leukaemia was treated with aminopterin. We regarded the occurrence of erythroblasts and thrombocytes in the blood during the treatment as first signs of a remission.

Abnormal proliferation of the reticulo-histiocytic system was, contrary to most descriptions in the literature, in our case not observed. The question as to whether or not the previous vaccination should be regarded as the cause or only as a stimulant to an already present latent disease, remains unanswered.

The normal structure of the marrow was not present. It differed from that of a leukaemic reaction, for which the original pattern of the blood-forming marrow tissue with its function and maturation zones is still recognisable. The complete absence of megakaryocytes also indicated a malignant process.

The infiltrations of erythroleukaemic elements in the intestines were probably responsible for the diarrhoea, which occurred just before death.

Summary

Description of a case of erythroleukaemia (morbus Di Guglielmo) in an infant of 7 months of age, where the symptoms manifested themselves shortly after smallpox vaccination. The patient had high fever, marked hepato-splenomegaly, anemia and thrombocytopenia as well as leucocytosis, with the occurrence of young, often atypical myeloid and erythroid elements in the blood. The erythroid elements dominated over the myeloid elements in the marrow. The treatment, consisting of aminopterin, supported by blood transfusions and antibiotics, did not influence the acute fatal development, although the young myeloid elements (myeloblasts, promyelocytes, and myelocytes) soon disappeared from the blood, and the liver and spleen grew smaller. At autopsy, erythroid and myeloid proliferation were found in the marrow, liver, spleen, lymphnodes, thymus and intestines.

Cas suraigu d'érythroleucémie traitée par l'aminoptérine.

Description d'un cas d'érythroleucémie (maladie de Di Guglielmo) chez un enfant de 7 mois, où les symptomes apparûrent peu après une vaccination antivariolique. Le malade avait une fièvre élevée, une hepato-splénomégalie importante, une anémie avec thrombocytopénie et leucocytose, et en raison de l'âge, il avait souvent des éléments atypiques myéloides et érythroides dans le sang. Les éléments érytroides étaient plus importants dans la moelle que les éléments myéloides. Le traitement, consistant en aminoptérine, renforcé par des transfusions sanguines et des antibiotiques, n'eu au-

cune influence sur l'issue fatale, bien que les éléments myéloides jeunes (myéloblastes, promyélocytes et myélocytes) aient disparus du sang, et que le foie et la rate aient diminués de volume. A l'autopsie, on trouva dans la moelle, le foie, la rates, les ganglions lymphatiques, le thymus et les intestins une prolifération érytroide et myéloide.

Ein mit Aminopterin behandelter Fall hyperakuter Erythroleukämie.

Beschreibung eines Falles von Erythroleukämie (Morbus Di *Guglielmo*) bei einem 7 Monate alten Kind, bei welchem die Symptome kurz nach der Pockenimpfung manifest wurden. Der Patient hatte hohes Fieber, deutliche Hepato-Splenomegalie, Anämie und Thrombocytopenie. Daneben Leukozytose mit jungen meist atypischen myeloischen und „erythroischen" Elementen im Blut. Letztere herrschten gegenüber den myeloischen Elementen im Mark vor. Die Behandlung in Form von Aminopterin, unterstützt durch Bluttransfusion und Antibiotica, beeinflusste den akuten fatalen Verlauf in keiner Weise, obwohl die jungen myeloischen Elemente (Myeloblasten, Promyelocyten und Myelozyten) bald aus dem Blut verschwanden und Leber und Milz kleiner wurden. Bei der Autopsie wurde eine Proliferation des erythropoetischen und myeloischen Gewebes in Knochenmark, Leber, Milz, Lymphknoten, Thymus und den Bauchorganen gefunden.

Caso hiperagudo de eritroleucemia tratado con aminopterina.

Se describe un caso de eritroleucemia (enfermedad de Di Guglielmo) en un niño de 7 meses de edad en el cual los primeros síntomas se manifestaron poco tiempo después de una vacunación antivariólica. El niño presentó fiebre elevada, pronunciada hepatoesplenomegalia, anemia y trombocitopenia asi como leucocitosis con presencia de jóvenes y frecuentemente atípicos elementos mieloides y eritroides en la sangre. Los elementos eritroides predominaban sobre los mieloides en la médula ósea. El tratamiento consistente en la administración de aminopterina ayudado con transfusiones de sangre y antibióticos no mostró ninguna influencia sobre el desarrollo agudo fatal de la enfermedad, aunque los elementos jóvenes mieloides (mieloblastos, promielocitos y mielocitos) desaparecieron rápidamente de la sangre y el hígado y el bazo se redujeron de tamaño. En la autopsia se encontró una proliferación eritromieloide en la médula, hígado, bazo, ganglios linfáticos, timo, e intestinos.

References

1. Benedetti G.: L'eritremia cronica. Haematologica, *19:* 229, 1938.
2. Bénard R. & Mallarmé J.: Un cas d'érythroleucémie aiguë remarquablement transformée par le sang conservé. Sang, *17:* 186, 1946.
3. Bussi L. & Franzini P.: Mielosi eritremica cronica con evoluzione terminale in mielosi emocitoblastica. Haematologica, *35:* 661, 1951.
4. Cooley T. B.: Brennemann's Practice of Pediatrics. Vol. III, 16, 1948, W. F. Prior Co, Hagerstown.
5. Denolin-Reubens R. & Delcourt R.: Un nouveau cas d'érythroleucémie. Acta haemat. *2:* 390, 1949.
6. Frada G.: Mielosi eritremica cronica. Haematologica, *35:* 225, 1951.
7. Guglielmo G. Di: Le eritremie. Haematclogica, *9:* 301, 1928.
8. —— Un nuovo caso di mielosi eritremica acuta (malattia di Guglielmo). Boll. Soc. Med. Chir. Cat. *5:* 588, 1937.
9. Guglielmo G. Di & Quattrin N.: Mielosi eritremica cronica. Haematologica, *24:* 1, 1942.
10. Harvier P., Le Melletier J., Lavergne G. H. & Lamotte M.: Erythroleucomyélose aiguë. Sang, *15:* 272, 1942—43.
11. Lazzaro G.: Mielosi eritremica acuta. Haematologica, *14:* 483, 1933.

12. LEITNER S. T.: Die intravitale Knochenmarksuntersuchung. B. Schwabe & Co, Basel, 1945, 1st ed.
13. LEMAIRE A. & MALLARMÉ J.: L'érythroleucomyélose, forme de transition entre la leucose aiguë et l'érythromyélose aiguë de Di Guglielmo. Sang, *15:* 213, 1942—43.
14. LOCASCIO R. & POSTIGLIONE F.: Un caso di mielosi eritremica acuta (malattia di Di Guglielmo). Haematologica, *33:* 289, 1949.
15. LÉVESQUE J., PERROT R. & BRISSET: Un cas d'érythroleucomyélose chez un enfant de 20 mois. Arch. franç. pédiat. *2:* 173, 1944—45.
16. MALLARMÉ J. & MOULONGUET A.: Étude sur la maladie de Di Guglielmo. Sang, *17:* 204, 1946.
17. MOESCHLIN S. & ROHR K.: Klinische und morphologische Gesichtspunkte zur Auffassung der Myelose als Neoplasma. Ergebn. inn. Med. u. Kinderh. *57:* 723, 1939.
19. PARADISO F. & REITANO R.: Studio clinico e anatomo patologico sulla malattia di Di Guglielmo. Haematologica, *20:* 947, 1939.
20. PITTALUGA G., LOEPER M., LEMAIRE A. & MALLARMÉ J.: Anémie érythroblastique de l'adulte. Ann. Méd. *46:* 368, 1940.
21. PARSONS L. G. & HAWKSLEY J. C.: The haemolytic (erythronoclastic) anaemias of late infancy and childhood. Arch. Dis. Childhood, *8:* 184, 1933.
22. RACHET, MALLARMÉ & BOUREL: Erythroleucomyélose à début purement érythroblastique. Sang, *22:* 582, 1951.
23. ROHR K.: Das menschliche Knochenmark. G. Thieme, Stuttgart, 1949, 2nd ed.
24. SARRAILHÉ A.: Erythroblastose aiguë de Di Guglielmo. Sang: *22:* 584, 1951.
25. STAHEL R.: Subakute Erythroleukämie ohne Splenomegalie. Helvet. med. acta, *10:* 605, 1943.
26. STORTI E.: Communications of the third International Congress of the International Society of Haematology, Cambridge, 1950.
27. WEIL P. E. & PERLÉS S.: La maladie érythroblastique de l'adulte. Ann. Méd. *43:* 5, 1938.
28. WHITBY L. & BRITTON C. J. C.: Disorders of the Blood. Churchill Ltd., London, 1947, 5th ed.

Received 15.4 1952

Binnengasthuis
Amsterdam

Acta Pædiatrica **42**: 166—167. March 1953

SUMMARY OF SUPPLEMENT

Gösta Tunevall: **Oto-Rhinological Infections in Childhood. (Acta Pædiat. 41. 1952. Suppl. 92.)**

The type characteristics of *H. influenzae* were studied. The typing procedure for encapsuled strains was improved e.g. by employing slide cultures for capsule swelling tests. The serological cross-reaction with encapsuled pneumococci, especially type 6, was confirmed. No hyaluronidase production could be demonstrated in *H. influenzae*.

The relations between encapsuled, converted rough, and primarily rough strains of *H. influenzae* were studied in transformation experiments. By varying the experimental conditions and watching carefully for all emerging variants, including noncapsulated ones, which were subsequently tested in new experiments, it was possible to transfer capsule formation ability and type specificity to a number of strains isolated in the non-capsulated state. No change of the antigenic composition of the bacilli could be observed, by gel precipitation experiments, in transformed strains, except that the acquisition of a capsular antigen was demonstrated.

The susceptibility of *H. influenzae* to six commonly used chemotherapeutics was investigated. Aureomycin, chloramphenicol, and terramycin were found most effective.

By the gel precipitation method, the presence in influenza bacilli of antigenic factors common to, or widely distributed within, the species was demonstrated. Unlike other tested bacteria, haemophilic organisms were easily dissolved by 1 % sodium carbonate solution, which was used for the preparation of an extract rich in the widely distributed antigenic factors.

The use of a sodium carbonate extract as the antigen of a complement fixation test (AHI) resulted in a reaction which, unlike tests used formerly for the recording of *H. influenzae* immunity, was fairly independent of the type and capsulation of the immunizing strains.

A convenient routine method for the determination of antipneumolysin (API) was worked out. No significant overlapping versus antistreptolysin was noted.

The transfer of APl, AS, AHI, and ASta from mother to foetus was studied. The transmission was more effective with regard to the antilysins than to the antibacterial complement fixing antibodies to *H. influenzae*.

The content of APl, AS, AHI, and ASta in infants and children of different

ages was found to be rising with increasing age, though with different rates for the separate antibodies.

Maxillary sinusitis was found on one or more occasions during one winter season in 60 % of apparently healthy children. Pneumococci and influenza bacilli were the prevailing pathogens, whereas staphylococci were comparatively rare. Haemolytic streptococci were never found. These observations deviated from most previous investigations and could be ascribed to the adequate methods used for collecting and examining the antral discharges. The antibody titers in nasal carriers of the separate pathogens were higher than in non-carriers but significantly increased only when the pathogens were present in inflamed sinuses. The importance of the immunization exerted by sinus processes is stressed.

In suppurative otitis, pneumococci were common in all ages up to seven years, while pyogenic staphylococci as primary pathogens were rare and largely restricted to infants and very small children. Influenza bacilli were frequent up to four years of age, and haemolytic streptococci increased their incidence with increasing age. This prevalence of different pathogens in the separate ages was paralleled by a corresponding difference in the evolution of the ability to produce antibodies to the same pathogens. The respiratory infection which generally preceded the otitis was found often to involve bacteria other than those found in the aural secretion. The *H. influenzae* otitis displayed a characteristic picture and tended towards recurrence. Further, the significance of age and of treatment for the occurrence of relapses was studied.

In the discussion, the pathogenicity of encapsuled influenza bacilli with regard to otitis is compared to that of non-capsulated strains. The main antibody titer levels and the antibody responses to acute infections in different ages are correlated to the variation according to age of the incidence of infections by the corresponding pathogens. The high antibody titers, and especially the high AHI rates, observed in maxillary sinusitis are discussed. The antibody production is pointed out as one of the factors which influence the course of infections and, with regard to otitis, the incidence of relapses.

Acta Pædiatrica **42**: 168—176. March 1953

PROCEEDINGS OF PEDIATRIC SOCIETIES

Proceedings of the Section for Pediatrics and School Hygiene of the Swedish Medical Society

Meeting at Boden, September 27, 1952.

R. Kostman: **Infant mortality in Norrland.**

M. Pehrson: **Infant myocarditis.**

Among the general symptoms of myocarditis, the feeding troubles (refusal to eat, vomiting attacks) are predominant. Often, the cardiac symptoms are so inconsiderable as to render a myocarditis verifiable only after repeated electrocardiographic examinations. During the years 1946—1951, at the Children's Department at Boden, 11 infants, aged from 15 days to 10 months, have been admitted with various types of myocardial damage. In four of these cases, this has probably been acquired intrauterinely. One of the four died. At autopsy, it was found to have a focal, subchronic myocarditis. In four children, the cardiac disease appeared in direct connection with infectious disease. The three remaining cases fell acutely ill, and died within 24 hours. In these latter cases, one being of the type of Fiedler's myocarditis, the autopsy disclosed a considerable cardiac enlargement with grave myocarditic changes.

Meeting, October 10, 1952.

R. Zetterström: **The structure of the bony tissue in Albers-Schönberg disease.**
(Together with B. Engfelt and A. Engström.)

The etiology of this often hereditary disease, characterized by osteosclerosis and grave anemia, is completely unknown. The purpose of the present investigation was to try to find out whether the bone salt has been changed in its ultra-structure and whether the bone is regenerated in the same way as a normal bone and, finally, whether the proportions of organic and inorganic bone substance reveal any changes from the normal. Biophysical methods, i.e. X-ray diffraction, microradiography and polarized light have been applied.

The investigations by means of X-ray diffraction showed that chrystallites have a normal orientation to the collagen. Nor has it been possible to ascertain by this method any changes from the normal in the molecular structure of the bone salt. The microradiograms show that, in Albers-Schönberg disease, the distribution of mineral salts differs entirely from that of normal bone. The medullary cavity is filled with calcified cartilage and bony tissue of a kind that is normally found only in the zone of growth of a bone. In the shaft of a long bone, outside this primitive tissue, a coarse-fibred, sparsely mineralized bony tissue corresponds to the osteophyte. Haversian systems, though never completely normal, are occasionally found. Nevertheless, the distribu-

tion of mineral salts suggests that even this primitive bone is subjected to regeneration; parts of new-formation, i.e. of a low content of calcium, alternating with parts subjected to resorption. This indicates that the disease cannot originate from diminished osteoclastic activity. The investigation in polarized light shows that the collagen is very irregularly arranged. The regular orientation of the basic organic substance of a normal bone is practically obliterated altogether. The collagen is found in bundles without any sort of system. In addition, the content of collagen varies considerably from one part of the bone to another. This should explain why this bone is much less strong than a normal bone, notwithstanding the enormous increase in the amount of bony tissue.

The investigation suggests, in the first place, that bone formed in the zone of growth may undergo regeneration but that it will not disappear. Consequently, no medullary cavity can be formed, while the cortical bone will contain bone of a primitive structure. It is impossible to state whether this depends on any special property in the bony tissue or on the tissue that normally should replace the bony tissue, i.e. the bone marrow.

Discussion:

B. Vahlquist. It was interesting to listen to a lecture in which the osteosclerotic process as such has been studied by modern technical methods. It is mostly the hematological changes that are discussed. I do not think that they can simply be explained as a "constriction" of the bone marrow, seeing that spongy bone remains. Perhaps some parallel disturbance in the blood-producing organ occurs? Similar observations can also be made in other connections, e.g., in certain forms of anemia in adults. It is advisable to take an X-ray picture of the skeleton in doubtful cases of anemia.

R. Lundström: **Rubella during pregnancy and its influence on the fetus.**
(Published in Acta Pædiatrica *41:* 583, 1952.)

B. Jonsson and E. Mannheimer: **Coarctation of the aorta with an early onset of decompensation.**

An account is given of 3 children, aged 8, 4 and 2 years, respectively, with coarctation of the aorta and early onset of cardiac insufficiency. Since it is now known that the late result is satisfactory in children, even after operation, it is important to have an early diagnosis of such cases. They should be operated on before any manifestation of hypertension or enlargement of the heart appears. The diagnosis is not difficult to establish clinically, provided the blood pressure is properly taken in the arms and legs.

Discussion:

K. O. Granström: In connection with the described cases, attention should be drawn to the observations made upon the fundus of the eye in cases of coarctation of the aorta that have been admitted to Södersjukhuset (Brit. Journ. of Ophth. 1951: 35: 143). In 24 out of 40 cases, a more or less pronounced spirally twisted sinuosity of the retinal arteries has been noticed, while other vascular changes (calibre variations and crossing phenomena), typical of ordinary hypertension, are either entirely missing or only observed to a minor degree. This appears to be of interest with regard to the

probable difference in origin of the high pressure in coarctation and in other forms of hypertension. For that reason, the question is asked whether an examination of the fundus of the eye has been performed upon the case series of the Pediatric Clinic. Most probably, a negative result has been reached, considering that the forementioned arterial sinuosity in the series was noted chiefly in cases above 20—25 years of age, and only occasionally in younger patients.

B. Jonsson: Because of the fact that small children with coarctation do not have any noteworthy hypertension, changes in the fundus of the eye are not often to be found. At the Pediatric Clinic of Karolinska Sjukhuset, the examinations of the fundus in cases admitted, during the year that the Hospital has been open, total 11. No pathological retinal changes have been noted.

R. Zetterström: **Mediastinal emphysema and spontaneous pneumothorax ("air-block") in newborn infants.**

Ever since the publication in 1937 of Wieland's investigations regarding the frequency of spontaneous pneumothorax (S.P.) in newborn infants, it has become a fairly generally accepted fact that this complication may occur rather often. Mediastinal emphysema (M.E.), on the other hand, is still regarded as rare. Occasionally, a case is published. Altogether, accounts of about 30 cases have been recorded.

Within a year, it has been possible to diagnose five cases of mediastinal emphysema and two with mediastinal emphysema and spontaneous pneumothorax. In all these cases, the syndrome has been fairly similar. Generally, the children have been asphyctic at birth, afterwards recovering and for a time behaving like normal newborn infants. After a free interval of a varying duration, the children have become acutely ill with cyanosis and dyspnoea and, in three instances, convulsions. The syndrome has been such as to suggest, in several cases, a diagnosis of intracranial injury at the delivery. In mediastinal emphysema, considerably weakened heart sounds have been a constant finding. The diagnosis has been determined after X-ray examination of the thorax. The frontal picture reveals a pneumothorax. For the diagnosis of mediastinal emphysema, a lateral picture is required. In such a picture, the substernal air accumulation is observed. In all the cases, the course has been benign.

The condition probably originates from bronchostenoses caused by aspiration. These stenoses produce a valvular mechanism with an increased distal pressure that leads to rupture and an interstitial or bullate emphysema. These emphysema may originate a mediastinal emphysema or a spontaneous pneumothorax according to the place of the leakage. One of the patients had, at the time of admission, a left-lateral pulmonary emphysema in the upper lobe, as well as a mediastinal emphysema. After 24 hours, the pulmonary emphysema had disappeared. Instead, a spontaneous pneumothorax had appeared. *Macklin* has experimentally produced a mediastinal emphysema by an increase in the intrapulmonary pressure. In the present investigation, a mediastinal emphysema was invariably preceded by an interstitial emphysema. The mechanism of origination is probably the same in the newborn child as in *Macklin*'s animal experiments.

Discussion:

John Lind: No mention has been made here of a disturbance that is, probably, of a central significance in the formation of the cyanosis, namely the partial redirection of the circulation, which is likely to happen often enough in the origination of a pneumothorax at the newborn period. The background of this occurrence is as follows:

During fetal life, the ductus arteriosus, as well as the foramen ovale, remain open, the circulation being turned right-left. At birth, the ductus arteriosus is, normally, immediately closed. However, the valve of the foramen ovale seems to be ajar during the first days of life. Further, its functional closure is more easily reversible than in the case of the ductus arteriosus. At birth, the right heart is, because of fetal circulation conditions, as equally developed as the left. During the first week of life, the differences in pressure between the right and the left heart should, accordingly, be comparatively small. Even insignificant rises in the pressure in the right auricle may, therefore, cause a right-left shunt through the foramen ovale to arise. Here is, probably, one of the chief causes of the cyanotic attacks during the first period of life. These conditions can be studied by angiocardiography. In normal cases, only a slight transfer of contrast medium from the right to the left auricle is noted at the foramen ovale during the first days of life. Conversely, in a penumothorax, a massive shunting occurs in the same direction, and this will happen even with a moderate pneumothorax. This may explain the often considerable cyanosis. The cyanosis seems to be completely disproportionate to the disturbance of the pulmonary function which is, as far as can be seen, insignificant.

B. Vahlquist: The high percentages of cerebral symptoms seem noteworthy. Can they be similarly dependent on air emboli?

Meeting, November 1, 1952.

Anna-Lena Bergström and Bertil Söderling: **Appetite and caloric requirements of so-called premature infants.**

A premature infant of some vitality often discloses signs of notable maturity and, sometimes, notwithstanding its occasionally extremely low weight, a functional development approximately corresponding to that of a fully developed child. The consumption of milk should be restricted to a rigid dietary control. If left free, an increased metabolism will occur, followed by a rapid initiation of the capacity to regulate temperature. It is unfortunate that a conception of degree of development like that of prematurity should be based simply on units of weight. Nor do researcher investigators make any distinction between prematurity and pseudo-prematurity. This must produce misleading results, in so far as the aim of an investigation is to show the difference between the immature and mature child.

J. Ström: **Penicillin treatment and immunity in scarlatina.**

B. Vahlquist: **Acute mononucleosis during the first years of life.**
(To be published in another connection.)

Yngve Larsson, **Stockholm: Acute complications in diabetes.**
(To be published in Acta Pædiatrica.)

B. Hellström and B. Jonsson: **Late prognosis in asphyxia neonatorum.**
(To be published in Acta Pædiatrica.)

M. d'Avignon & I. Keilson: **Electro-encephalographic findings in children previously treated under a diagnosis of asphyxia neonatorum.**
(To be published in Acta Pædiatrica.)

L. Gyllensten—B. Hellström: **Eye changes in the young of mice reared in an oxygenated atmosphere. (Reported by Gyllensten.)**

(Published in Acta Pædiatrica *41:* 577, 1952.)

Discussions:

R. Zetterström: The investigations that have just been submitted here show convincingly that changes, similar to those occurring in retrolental fibroplasia, can be experimentally produced by means of a high oxygen concentration. The lecturer also suggested as a hypothesis that the lumen of the retinal vessels would decrease from the high oxygen concentration, thus causing a local anoxia. *Nisell* has shown that, with a high oxygenation, the lumen of the arterioles of the lungs is diminished. In premature children with slight anoxia, owing to deficient regulation of respiration, the ductus arteriosus has been found to be functionally open even two or three weeks after birth. In severe anoxia, the ductus arteriosus can remain open in fully developed children. By means of cardiac auscultation and phonocardiography, it has been possible to show that a patent ductus arteriosus closes when the oxygenation is increased by the addition of pure oxygen. When the oxygen saturation is decreased the ductus arteriosis again opens. By means of cardiac catheterization, *Bengt Jonsson* has been in a position to demonstrate the presence of a shunt from left to right. On the other hand, when the oxygenation is increased, the shunt vanishes. The closure of the ductus arteriosus should, accordingly, be due to the degree of oxygenation.

In low-weight premature infants, the hyaloid artery remains patent at birth. It is likely to provide nutrition for the peripheral portions of the retina. At this stage of development, the retinal vessels have not, as yet, their full range. After birth, the oxygenation normally rises, on account of the rearrangement of the circulation. When oxygen is administered at a high concentration, a further rise in the oxygenation will be obtained, as well as physically dissolved oxygen in the blood. This abnormally high oxygenation in a prematurely born child can be presumed to exert the same influence on the hyaloid artery as on the ductus arteriosus, i.e. bring about a closure of the vessel, thus causing the peripheral part of the retina to become anoxic. Nevertheless, as long as the child lives in an atmosphere of high oxygen saturation, the content of oxygen in the blood is great enough to allow diffusion into the extracellular fluid an amount of oxygen sufficient for the nutrition of the retinal tissue. On the other hand, when the oxygen content in the atmosphere in which the child lives is reduced, the retinal tissue will no longer obtain enough oxygen for its nutrition. A destruction of tissue will then occur.

R. Lagercrantz: **Studies of antibodies in BCG vaccinated and tuberculous children.**

(To be published in Acta Pædiatrica.)

B. Hagberg: **The capacity of serum to bind iron in healthy and sick children.**

The total iron-binding capacity in serum of infants and children in health and disease

The total iron-binding capacity (according to the method of Rath & Finch) and the serum iron (according to Vahlquist) were determined in serum from 200 healthy infants and children and about 100 with various diseases, preferably infections. The

mean values in the normal cases at different ages are recorded below. The investigations are to be published in detail in Acta Pæd. Suppl. 93.

Normal values of the total iron-binding capacity (TIBC) and the serum iron (SI) at various ages

	TIBC	SI
Umbil. cord	259 ± 10.5	173 ± 6.9
½—2 months	212 ± 6.6	142 ± 7.1
2—4 »	308 ± 11.3	113 ± 5.6
4—6 »	360 ± 12.5	78 ± 6.1
6—12 »	394 ± 13.4	93 ± 6.5
1—3 years	387 ± 9.7	99 ± 5.9
3—7 »	368 ± 9.6	124 ± 8.7
7—14 »	353 ± 7.6	119 ± 6.7
Adults	330 ± 4.9	130 ± 5.2
(Women at term)	(470 ± 15.3)	(98 ± 6.7)

B. Broman: **Intramuscular blood injections.**

G. Ekström & T. Möller: **Electrocardiograms in ductus arteriosus persistens.**

R. Zetterström: **The heart volume during the newborn period.**

(Together with *S. R. Kjellberg* and *U. Rudhe.*)

According to published observations, an enlargement of the heart of a newborn child will occur, not only in the case of organic cardiac abnormalities, but also in connection with sequelae of various morbid conditions, such as asphyxia neonatorum with extensive pulmonary atelectases and morbus hemolyticus neonatorum, as well as when diabetes mellitus is present in the mother. It has also been noticed that the heart volume decreases during the new-born period. Nevertheless, so far no account has been given of the rapidity with which such a reduction in the heart volume takes place or of the extent of the decrease.

35 children without any clinical symptoms have been examined, each child three times, during their first week of life. As in later life, the first 24 hours disclose a good correlation between heart volume and body weight. After birth, a decrease in the heart volume takes place. It reaches a minimum during the fifth day of life. On an average, the decrease is of about 25 per cent. The absolute figures for the first, third, fifth and sixth day of life are 48, 40, 35 and 37, respectively. The difference between the first and third day is statistically significant. The reduction in the heart volume is probably due to the disconnexion of the placental from the maternal circulation, the redirection of the circulation and the initial decrease in weight.

In neonatal asphyxia, the heart volume may, even in the first 24 hours of life, be abnormally increased. The volume does not decrease, to any noteworthy degree, as long as the symptoms remain. The explanation of the increased heart volume has to be looked for in a circulation insufficiency originating in a condition of anoxia. Severe cases of morbus hemolyticus neonatorum have, likewise, revealed a statistically significant increase in the heart volume. Also in this instance, the increase is probably due to a circulation insufficiency, caused by anoxia, as well as by the increase in the blood volume ascertained by *Mollison* in that disease. A similar rise in the heart volume is also found in edematous and affected children born of mothers with diabetes

mellitus. In all these three morbid conditions, the heart volume falls to values normal in relation to the weight, after the abatement of the morbid symptoms connected with the adaptation to an extra-uterine life.

Discussion:

J. Lind: The pathologists have also found a diminution in the weight of the heart during the first period of life. The heart volume is closely correlated to the body weight. The body weight at birth and the weight of the placenta might, then, be expected to yield a quotient with the heart volume closely conforming to that of the heart volume and body weight when, on the 6th—8th day, an adaption has been achieved to the extra uterine circulation. A study of the heart volume during the first week of life seems to show that the voluminal decrease occurs chiefly during the first 24 hours. No notable difference in the heart volume is to be found from the 2nd to the 6th—8th day. The heart volume is closely correlated to the blood volume. It is, therefore, worth noting that the blood volume does not decrease but retains a constant level during the first week of life, in spite of falling hemoglobin values (as investigated by *Sjöstrand*'s methods together with *S. Iggbom* and *P. Karlberg*). It is, of course, difficult to show whether any dilatation of the heart occurs in atelectases, and such conditions as may be supposed to put a load on the heart. The best way, probably, is to determine by X-rays the size of the heart immediately after birth, and afterwards at equal intervals. Such a serial investigation in four "normal" cases was reported, as well as in two cases of asphyxia, both with radiological evidence of atelectases. Both the asphyxia cases show a cardiac dilatation which after only two hours seemed to be abating. In one of the cases, the heart volume had, on the third day of life, fallen to a value below that at birth. In the other case, this happened only on the fifth day. These two cases may, possibly, represent a disturbance to which, so far, sufficient attention has not been paid; cor pulmonale acutum neotorum.

E. Jacobsson: Neoteben, iso-nicotinicacidhydrazide (INH) in tuberculous meningitis.

At Samariten, a boy of 9 years with tuberculous meningitis was treated with this preparation. He was given streptomycin with an initial improvement, followed by a change for the worse. After an administration of INH, a certain improvement occurred, but only after an increase of the dosage to 10 mg/kg of body weight could any definite alleviation of the symptoms be noted. The dosage was gradually raised to 16.7 mg/kg, given during 4 months without any toxic by-effects whatever being manifested. During that time, he was entirely free from symptoms. He was discharged as healthy 6 months after the beginning of the treatment, including 1 month during which no treatment with INH had been given.

Discussion:

R. Lagercrantz: In September last, I had occasion to take part in a seminary in Paris on the subject of antibiotic therapy. INH occupied the centre of interest. Paediatric case series were reported from, inter alia, Professor Debré's and Professor Fanconi's Clinics. It was generally agreed that this drug is useful, but that it should not be used alone, since the risk of the appearance of resistant strains is very great. A combination with streptomycin and PAS, or one or the other of the two, was regarded as the method of choice. In meningitic cases, all the three substances were

administered together at Debré's Clinic. INH was looked upon as very valuable addition to the medical arsenal. There is justification for hoping, it was stated, that it would now prove possible to reduce the early mortality in tuberculous meningitis.

H.-O. Mossberg: **Dosages of chloromycetin palmitate.**

A dose of chloromycetin palmitate must be three times that of chloramphenicol, in order to produce the same maximal blood concentration. To maintain a blood concentration of chloromycetin of about 10 μg/ml, 50 mg/kg × 4 of chloromycetin palmitate are required. For the purpose of obtaining a more rapid initial rise in the blood concentration, the first dose of chloromycetin palmitate should be combined with a small one-time dose of chloramphenicol (about 25 mg/kg). At the present prices, the chloromycetin palmitate is 3 times as expensive to use as ordinary chloromycetin (chloramphenicol).

R. Lundström and T. Johnsson: **Hyperimmune serum in prophylaxis and therapy in pertussis.**

According to official Swedish statistics, during the five-year period of 1946—50, 165 children died from pertussis. One hundred and twenty-nine, or 78 per cent, of these children were under 1 year of age. Through a more extensive use of vaccination with triple vaccine, started as early as at an age of 3 months, the risk of infants falling ill will, probably, diminish considerably. Unvaccinated infants must, however, still be expected to be exposed to contagion from brothers and sisters or at nursery homes. The risk of onset of the disease after a family contact can be estimated at 70—80 per cent. With convalescent, or so-called hyperimmune serum (prepared from the blood of donors inoculated against pertussis), it seems possible to bring the risk down to 20—30 per cent. The course of the diesase is, in such cases, as a rule less malignant than without this protection. The experience of the present authors confirms this. The results of treatment appear extremely uncertain, when the disease has already broken out. The big doses of hyperimmune serum that have to be administered, 25 ml, are inconvenient. For this reason, they have been fractionated (KABI), the active gamma globulin fractions being isolated and produced in a solution. This is obtainable from the State Bacteriological Laboratory and called "Immunity globulin in pertussis", in doses of 2.5 ml, corresponding to 25 ml of serum.

Discussion.

B. Vahlquist: The hyperimmune serum is a great boon in pertussis. The price is, however, a drawback. Cutter's "Hypertussis" costs 57.90 kronor. In Sweden, a society for sick-relief pays 50 per cent of the cost of medicines. In my opinion, serum must be regarded as a medicine not only when given therapeutically in a disease already in progress but also when given on suspicion after exposure.

G. Hackzell and A. Bergstrand: **Cases of congenital cerebral tumours.**

At Samariten, a case of congenital cerebral tumour has recently been treated. It occurred in a girl with a weight at birth of 2.780 gm, a first child of young parents. The patient was born four weeks before the expected date. At birth, the circumference of the head measured 34 cm. It rapidly increased. On the second day of life, it measured 38 cm. The fontanels were tense and curved, the sutures forced apart. She was

not active, her hands and feet were cyanotic. The veins above the right temporal region were large and tense. After 24 hours, repeated attacks of tonic convulsions were noted. Her condition deteriorated. She died when 2 days old. Postmortem examination disclosed a big tumour of ependymoma type in the right hemisphere of the cerebrum. Among numerous accounts of cerebral tumours in children, we have come across only two cases where it has been possible to state definitely that the tumours were congenital, disregarding for the moment dermoid cysts and teratomas which are mostly looked upon rather as malformations. In 1933, *Russel* and *Ellis* described a case of glioma in a stillborn child. In that instance, a relative obstruction to delivery was probably caused by the big size of the head. Patho-anatomically the tumour was defined as a spongioblastoma. The other case was reported by *Wallace* in 1948. It occurred in a child, three weeks old. In this instance, a note had been made at the time of birth that the head was big. A severe hydrocephalus developed rapidly followed by convulsions. The child died at the age of three weeks. The postmortem examination revealed a medulloblastoma. In 1934, *Gross* presented a comprehensive record of such early cerebral tumours as have been described in the literature from as far back as 1861, when a case of intracranial dermoid cyst in a two months old child was published. The latest case of genuine cerebral tumour (i.e. not dermoid cyst or teratoma), of which *Gross* found a description, referred to a child, seven weeks of age, with a gliosarcoma. A diagnosis of cerebral tumour is invariably difficult to determine in infants. In practically all cases, hydrocephalus and convulsions are noted. In our present case, the venous stasis in the temporal region was the sole sign of a local process, and not a hydrocephalus of an ordinary type.

L. Garby: **Wissler's syndrome.**

Wissler's syndrome (subsepsis allergica Wissler) is reviewed from a scrutiny of the literature. Three cases are described one of which was successfully treated with ACTH.

Acta Pædiatrica 42: 177. March 1953

BOOK REVIEW

N. B. Talbot, Edna H. Sobel, Janet W. McArthur and *J. A. Crawford: Functional endocrinology.* From birth through adolescence. Harvard University Press, Cambridge 38, Mass., U.S.A. 1952. Price $ 10.00.

This new textbook of paediatric endocrinology has a very appropriate title: Functional Endocrinology. The nine chapters, each dealing with an endocrine gland, have been divided in two parts. In the first called "basic considerations" the authors give a review of the clinical physiology of the glands and of methods for appraising its status. The second part of each chapter, "clinical consideration," deals with the glandular diseases and includes typical case histories.

The "basic considerations" are of a great value not only to the paediatric endocrinologist but to all who are interested in clinical physiology. In a clear and concise way the authors give information concerning the role of endocrine glands in health and ordinary diseases. It is natural that in a book of this type a certain condensation of facts is necessary and that the reader is not always willing to subscribe to the authors opinion. However this is of minor importance, the main thing is the amount of valuable facts, which to a certain extent have not been published previously. The clinical parts, in the more conventional sense, have been distributed over several chapters. This disadvantage has been overcome by cross references but makes these parts of the book less easy to read than the "basic considerations." An appendix gives the normal values for laboratory procedures. "Functional Endocrinology" will prove a very useful book in paediatric work.

Carl Gustaf Bergstrand Stockholm.

A. Low: Growth of Children.

The University Press, Aberdeen, 1951. Price 10 s.

The late Alexander Low when Professor of Anatomy at the University of Aberdeen in 1923 to 1927 made anthropographical measurements on a number of children. His records have now been published from the Anatomy Department by professor R. D. Lockhart with collaborators. In all 66 boys and 60 girls were measured, each one at 6 different ages (3 days, 1, 2, 3, 4 and 5 years of age) and at each examination 28 different measurements were taken, totaling 20,000 measurements. These are tabulated in 56 tables. No consideration has been paid to the mental development of the children nor to the incidence and influence of temporary or more chronic illnesses.

Acta Pædiatrica **42**: 178. March 1953

NEWS AND COMMENTS

The *VII International Congress of Pediatrics* will be held in Havana, Cuba, October 12—17, 1953. Professor Felix Hurtado, Cuba, is President.

According to the preliminary programme supplied by the Organizing Committee of Havana there will be 5 Plenary Sessions. The principal subjects chosen for discussion are: I. "*Epilepsy in Infancy and Childhood*". Reporters: Ahlström (Sweden) and McQuarrie (U.S.A.). Co-reporters: Lennox (U.S.A.), Penfield (Canada), Perlstein (U.S.A.) and Escardó (Argentine). II. "*Diagnosis of Congenital Malformations of the Heart and great Vessels susceptible to Surgical Treatment*". Reporters: J. Lind (Sweden), Chávez (Mexico). Co-reporters: Gibson, Steinberg, Taussig and Gassul (U.S.A.), Kreutzer (Argentine). III. "*Problems concerning the Premature Infant*". Reporters: Ylppö (Finland) and Clement Smith (U.S.A.). Co-reporters: Lelong (France), Poleri (Uruguay), Moncrieff (England), Vahlquist (Sweden), and Rominger (Germany). IV. "*Primary Tuberculosis and its Complications*". Reporters: Wallgren (Sweden) and Lincoln (U.S.A.). Co-reporters: Debré (France), Cocchi (Italy), Graham (Great Britain) and Scroggie (Chile). V. "*Metabolism and Nutrition*". Reporters: György and Darrow (U.S.A.). and Fanconi (Switzerland). Co-reporters: Ramos (Spain), Frontali (Italy), Gómez (Mexico), and Krumdieck (Peru).

In addition to these 5 Plenary Sessions there will be 3 Round Table Discussions in the afternoons of October 13, 14, and 15: The subjects that will be treated and the Chair-men of the Round Table are: 1. "*BCG-Vaccination*". (A. Wallgren, Sweden), 2. "*Nephrosis in Children*". (H. Smith, U.S.A.), 3. "*Bacteriology in Infantile Diarrhoea*" (Adams, Germany), 4. "*Antibiotics*" (H. Poncher, U.S.A.), 5. "*Virus Diseases*" (Stokes Jnr., U.S.A.), 6. "*Neoplastic Diseases*" (S. Farber, U.S.A.), 7. "*Problems of Hematology*" (Diamond, U.S.A.), 8. "*Pediatric Surgery*" (J. Lozoya, Mexico), 9. "*Pediatric Endocrinology*" (Bronstein, U.S.A.).

At an Extraordinary Session on October 14 (Silver Aniversary of the Cuban Pediatric Society) the following speakers have been invited to deliver special lectures: E. Galán (Cuba), R. Debré (France), H. Helmholz (U.S.A.) and M. Suárez (Spain).

Only one session is scheduled for free subjects. The number of papers that can be accepted is limited to 20. There will be an opportunity of showing exhibits and films. Those who intend to make use of this opportunity as well as those who wish to read a paper on a free subject should send the title of the paper or the exhibit and/or the film to the Organizing Committee before June 1, 1953. Address: Hospital "Mercedes". L.Y. 21, Vedado, La Habana, Cuba.

Prof. G. Fanconi, Kinderspital, Zürich (Switzerland) is General Secretary of the International Pediatric Association.

The American Academy of Pediatrics has scheduled a Meeting in Miami October 2—9, 1953.